



PHD

Ruthenium Catalysed Transformations of Amines and Alcohols

Watson, Andrew

Award date:
2011

Awarding institution:
University of Bath

[Link to publication](#)

Alternative formats

If you require this document in an alternative format, please contact:
openaccess@bath.ac.uk

Copyright of this thesis rests with the author. Access is subject to the above licence, if given. If no licence is specified above, original content in this thesis is licensed under the terms of the Creative Commons Attribution-NonCommercial 4.0 International (CC BY-NC-ND 4.0) Licence (<https://creativecommons.org/licenses/by-nc-nd/4.0/>). Any third-party copyright material present remains the property of its respective owner(s) and is licensed under its existing terms.

Take down policy

If you consider content within Bath's Research Portal to be in breach of UK law, please contact: openaccess@bath.ac.uk with the details. Your claim will be investigated and, where appropriate, the item will be removed from public view as soon as possible.

Ruthenium Catalysed Transformations of Amines and Alcohols

Submitted by Andrew John Alfred Watson

For the degree Doctor of Philosophy

University of Bath, Department of Chemistry

September 2011

COPYRIGHT

Attention is drawn to the fact that copyright of this thesis rests with its author. This copy of the thesis has been supplied on condition that anyone who consults it is understood to recognise that its copyright rests with its author and that no quotation from the thesis and no information derived from it may be published without prior written consent of the author.

This thesis may be made available for consultation within the University Library and may be photocopied or lent to other libraries for the purposes of consultation.

Signed..... Date.....

CONTENTS	
ACKNOWLEDGEMENTS	iii
SYNOPSIS	v
ABBREVIATIONS	vi
1 INTRODUCTION	1
1.1 C-N Bond Forming Borrowing Hydrogen Reactions	1
1.2 C-C Bond Forming Borrowing Hydrogen Reactions	16
1.3 References	25
2 RESULTS AND DISCUSSION I	32
2.1 Background	32
2.2 Initial Studies	32
2.3 Reaction Scope	39
2.4 Chapter Summary	43
2.5 References	44
3 RESULTS AND DISCUSSION II	48
3.1 Background	48
3.2 Initial Studies	48
3.3 Reaction Scope	51
3.4 Chapter Summary	57
3.5 References	58
4 RESULTS AND DISCUSSION III	61
4.1 Background	61
4.2 Initial Studies	61
4.3 Reaction Scope	68
4.4 Chapter Summary	76
4.5 References	77

5	RESULTS AND DISCUSSION IV	80
5.1	Background	80
5.2	Initial Studies	80
5.3	Reaction Scope	83
5.4	Chapter Summary	90
5.5	References	91
6	RESULTS AND DISCUSSION V	94
6.1	Background	94
6.2	Initial Studies	95
6.3	Reaction Scope	108
6.4	Chapter Summary	113
6.5	References	114
7	EXPERIMENTAL	116
7.1	General Experimental Methods	116
7.2	Experimental Procedures: Chapter 2	117
7.3	Experimental Procedures: Chapter 3	128
7.4	Experimental Procedures: Chapter 4	140
7.5	Experimental Procedures: Chapter 5	157
7.6	Experimental Procedures: Chapter 6	177
7.7	Relevant NMR Spectra	195
7.8	References	203
	APPENDIX	207
	Publications to date	

ACKNOWLEDGEMENTS

Firstly I wish to thank Professor Jonathan Williams (JM JW) for giving me the opportunity to come to Bath and join his research program, for which I will always be grateful. His help, support, time and ideas have been greatly appreciated. Whilst I may not have always listened, I hope that the end result has been what he wanted. I'd particularly like to thank Jon for just letting me get on with the work and allowing me to generate my own ideas, following them up and publishing, in particular. I would like to thank him for letting me write my own articles, without which, this thesis would have been much more difficult and time consuming activity.

Next I would like to thank all the people who have helped me through the Pharma-Synthesis Network. I would also like to thank all those at GSK who offered ideas, made me feel like one of the team and offered help when it was needed, in no particular order; Dr. Vipul Patel, Gail Fisher, Dr. Steve Swanson, Steve Richards, Sebastian Campos, Niall Anderson, Charlotte Mitchell, Tony Cooper, Ian Campbell, Natalie Wellaway, Ian Smith, Dr. John Harling, John Pritchard and Dr. Andy Bewster.

I would particularly like to thank Dr. Aoife Maxwell for her part in guiding me as a student, an independent researcher and a job seeker. Without her, I would have been much further behind and still looking for a job. Her input into the projects I have run has been invaluable and her focus has kept me on track. I am grateful beyond words, as I know that this thesis and my new job are because of her help. Finally, I'd like to thank Chris, Gerry and Charlotte for helping me prepare for interview, chemical discussions and the enthusiasm to keep searching for new chemistry to do. I hope that we will meet again soon.

I'd like to thank the JM JW group past and present for making Bath such a great place in which to work. Particular thanks go to Tracy and Hannah for being constant sources of help, advice and listening to my mad new ideas. I would particularly like to thank them for their help with proof reading, without which I am sure there would be far more mistakes in this thesis. To the rest of the group past/present/future in no particular order: Nathan, Haniti, Simon, Nikki, Hannah, Mike, Liana, James, Russ, Jim, Sim, Dom and Ben, many thanks for all the good times and bad.

I would also like to thank the members of the Bull group past and present for providing milk, tea, sadly not so much sugar, but friendship. They are in no particular order: Iwan, Paul, Rob, Caroline, Jen and Lucy.

I am indebted to the support workers and technical staff of the department, with particular mention going to Dr. John Lowe and Dr. Anneke Lubben for their constant help with NMR and mass spectrometry analysis. Without these people, there would be no data, no results and therefore no work.

I'd like to thank the Morris family, especially my girlfriend, Chrissy for support and an ear to listen to all my moans, groans and chemistry rubbish, Lyn for constant cups of tea and sandwiches whilst writing my thesis and Clare for letting me use her car to get to work occasionally.

Finally, I would like to thank my parents for their constant support in anything I chose to do, both emotionally and financially. I would also like to thank the IRB for not scheduling any England rugby world cup matches on a weekday.

SYNOPSIS

This thesis describes the chemistry developed during a study of ruthenium catalysed reactions of amines and alcohols.

Chapter 2 describes a one-pot two-step process to access primary amines using borrowing hydrogen methodology with masked ammonia sources. This unique approach allows selective access to primary amines without the over alkylation seen when using other ammonia sources. Furthermore, the borrowing hydrogen reaction can be coupled with an *in-situ* palladium catalysed hydrogenolysis/deprotection to afford primary amines.

Chapter 3 describes the modification of an existing ruthenium catalysed borrowing hydrogen reaction to allow the synthesis of cyclic tertiary amines from diols. This improved system has a lower catalyst loading than previously reported and has been applied to a wide range of substrates.

Chapter 4 focuses on attempts to improve the existing ruthenium catalysed C-N bond forming reactions by reducing the reaction time, reaction temperature or catalyst loading. A comparison of structurally related catalysts already present in the literature, using ionic liquids as an alternative reaction solvent and the application of microwave heating is described.

Chapter 5 details a novel application of benzylic alcohols in a tandem oxidation/C-H activation process. Further exploration of the chemistry resulted in a three-step one-pot oxidation/C-H activation/reduction procedure resulting in alkylated benzylic alcohols. This three-step process demonstrates the use of ruthenium in three fundamentally different catalytic processes back to back.

Chapter 6 details the application of nucleophilic aromatic substitution with borrowing hydrogen, hydrogen transfer and a successful tandem isomerisation/substitution. The reaction scope including the nucleophile, reaction solvent, suitable catalyst and electrophile were all evaluated, resulting in specific reaction conditions for a range of para-fluoro substituted aromatic vinylic and allylic alcohols.

ABBREVIATIONS

Å	- Angstroms
API	- Active pharmaceutical ingredient
Ar	- Aryl
atm	- Atmospheres
b. p.	- Boiling point
BARF	- Tetrakis(3,5-bis(trifluoromethyl)phenyl)borate
BIPHEP	- 2,2'-Bis(diphenylphosphino)-6,6'-dimethoxy-1,1'-biphenyl
BINAP	- 2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
[BDMIM][PF ₆]	- 1-Butyl-2,3-dimethylimidazolium hexafluorophosphate
Bn	- Benzyl
[BMIM][BF ₄]	- 1-Butyl-3-methylimidazolium tetrafluoroborate
[BMIM][Cl]	- 1-Butyl-3-methylimidazolium chloride
[BMIM][OTf]	- 1-Butyl-3-methylimidazolium triflate
[BMIM][PF ₆]	- 1-Butyl-3-methylimidazolium hexafluorophosphate
[BMIM][SbF ₆]	- 1-Butyl-3-methylimidazolium
<i>n</i> -Bu	- <i>n</i> -Butyl
<i>t</i> -Bu	- <i>tert</i> -Butyl
<i>t</i> -BuOH	- <i>tert</i> -Butanol
cod	- 1,5-Cyclooctadiene
coe	- cyclooctene
cot	- 1,3,5,7-Cyclooctatetraene
Cp [*]	- Pentamethylcyclopentadienyl
Cy	- Cyclohexyl

DABCO	- 1,4-Diazabicyclo[2.2.2]octane
DIOP	- 2,3- <i>o</i> -Isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane
dippf	- 1,1'-Bis(diisopropylphosphino)ferrocene
DMAc	- Dimethylacetamide
DME	- Dimethoxyethane
DMF	- <i>N,N</i> -Dimethylformamide
DMSO	- Dimethylsulfoxide
DPEphos	- (Oxydi-2,1-phenylene)bis(diphenylphosphine)
dppf	- 1,1'-Bis(diphenylphosphino)ferrocene
dppb	- 1,4-Bis(diphenylphosphino)butane
dppbe	- 1,2-Bis(diphenylphosphino)benzene
dppe	- 1,2-Bis(diphenylphosphino)ethane
dppm	- Bis(diphenylphosphino)methane
dppp	- 1,3-Bis(diphenylphosphino)propane
dpppent	- 1,5-Bis(diphenylphosphino)pentane
ee	- Enantiomeric excess
EI	- Electron impact
h	- Hours
Hünig's Base	- <i>N,N</i> -Diisopropylethylamine
Hz	- Hertz
IR	- Infrared
<i>i</i>	- <i>Iso</i>
<i>J</i>	- Coupling Constant

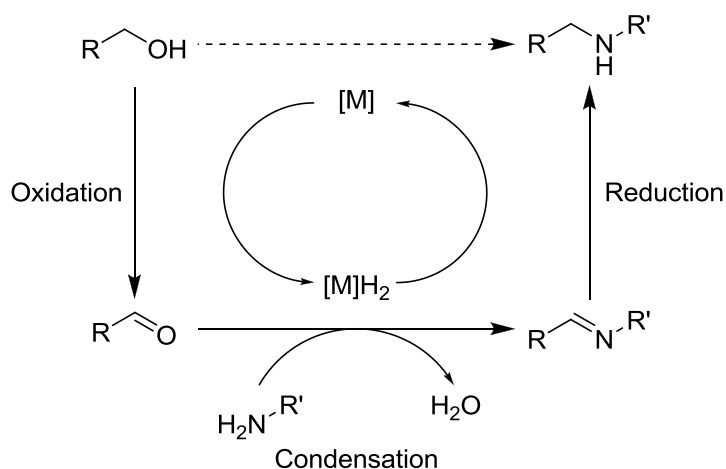
<i>m</i>	- Meta
Me	- Methyl
MeOH	- Methanol
Mes	- 1,3,5-Trimethylphenyl (mesityl)
min	- Minutes
MIBK	- Methyl Isobutyl Ketone
m. p.	- Melting point
MS	- Molecular Sieves
MW	- Microwave
<i>p</i> -MeOC ₆ H ₄	- <i>p</i> -Methoxyphenyl
NMR	- Nuclear Magnetic Resonance
<i>o</i>	- Ortho
<i>p</i>	- Para
PG	- Protecting Group
Ph	- Phenyl
PPh ₃	- Triphenylphosphine
ppm	- Parts per million
<i>i</i> -Pr	- <i>iso</i> -Propyl
<i>n</i> -Pr	- <i>n</i> -Propyl
r. t.	- Room temperature
SES-NH ₂	- 2-(Trimethylsilyl)ethanesulfonamide
Tf	- Trifluoromethanesulfonyl
TFA	- Trifluoroacetic acid
THF	- Tetrahydrofuran

TMS	- Trimethylsilyl
TLC	- Thin Layer Chromatography
Tol	- Toly (methylphenyl)
Triphos	- Bis(diphenylphosphinoethyl)phenylphosphine
UV	- Ultraviolet
Xantphos	- 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene

1 INTRODUCTION

1.1 C-N Bond Forming Borrowing Hydrogen Reactions

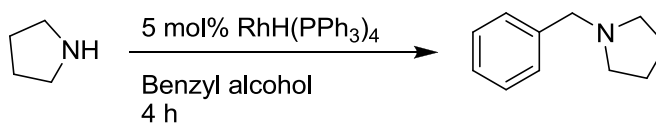
Alcohols have a limited range of reactivity and require either activation or oxidation to facilitate substitution reactions due to the poor electrophilicity of most alcohols. However, because of this, alcohols are stable and widely available. Oxidations usually require stoichiometric metal reagents, however, more catalytic methods are being applied and the use of the mild Swern oxidation is present in many routes to pharmaceuticals. The activation of alcohols involves conversion into halides or sulfonates on scale, both of which require an extra step which generates more waste and results in poor atom economy. More importantly, most alkyl halides and sulfonates are classified as genotoxic and the pharmaceutical industry is required to control these compounds to extremely low levels in APIs for patient safety. It follows that any methodology that avoids the need to convert alcohols to halides or sulfonates will offer significant benefits to both industry and synthesis. The equivalent carbonyl compound, on the other hand, is much more reactive, allowing a broader range of reactions to be conducted. This increased reactivity however, is a trade-off, as the carbonyl compounds are prone to decomposition due to the increased reactivity and are often difficult to form selectively, i.e. without over oxidation. An ideal system would allow the use of stable, non-toxic alcohols while maintaining the reactivity of the carbonyl compound. One way to achieve this is known as Borrowing Hydrogen, where an alcohol is temporarily oxidised by a catalyst to a carbonyl compound, which undergoes a condensation reaction with a nucleophile, before being reduced by the same catalyst that performed the oxidation, all in one pot (Scheme 1).



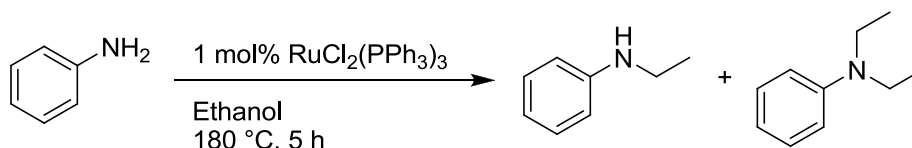
Scheme 1 - Borrowing Hydrogen Methodology

Many different examples of Borrowing Hydrogen have been used successfully, and this chapter will illustrate the wide variety of applications and catalysts available.

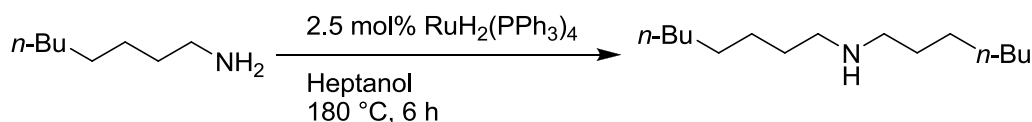
Grigg



Watanabe



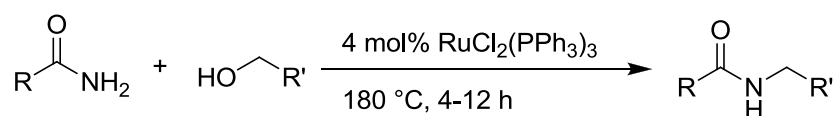
Murahashi



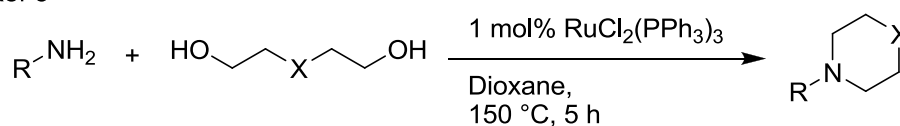
Scheme 2 - Early Examples of Borrowing Hydrogen

The first reports of borrowing hydrogen can be attributed to two authors; Grigg (who used a rhodium catalyst¹) and Watanabe (ruthenium²) who independently reported the *N*-alkylation of amines with alcohols in 1981. Murahashi also reported the alkylation of amines with alcohols using an alternative ruthenium³ catalyst a year later (1982). These first reports (Scheme 2) demonstrated that noble metals such as rhodium, ruthenium and later iridium could catalyse borrowing hydrogen reactions.

Ref 4



Ref 5

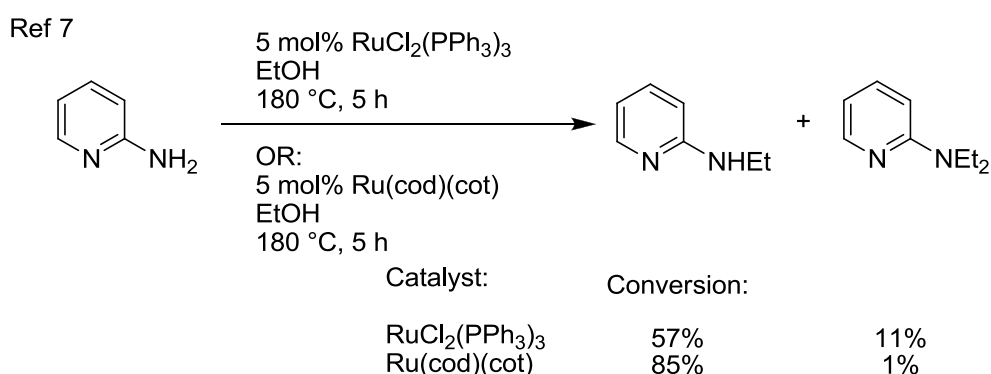


Where X = O, CH₂, NMe, NEt, NPh

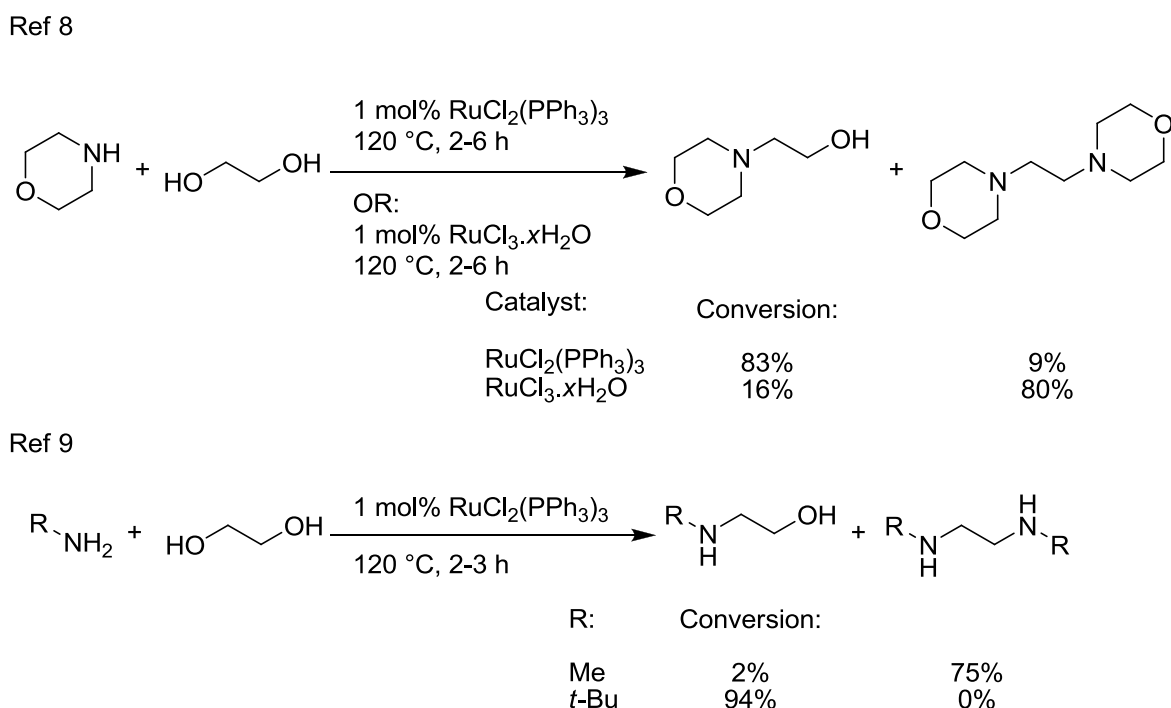
Scheme 3 - *N*-Alkylation of Primary Amides and *N*-Heterocyclization of Diols

The initial work demonstrated the principal, but suffered from a lack of selectivity, with both secondary and tertiary amines being formed, and harsh reaction conditions (180 °C). However, this did not stop Watanabe from expanding the scope of the catalyst to include the synthesis of secondary amides⁴ and cyclic tertiary amines⁵ (Scheme 3).

Watanabe was able to tune the reaction conditions to selectively form either secondary or tertiary amines from primary amines by altering the stoichiometry⁶ and later applied similar conditions to the *N*-alkylation of aminopyridines⁷ (Scheme 4).



Scheme 4 - Selective *N*-Alkylation of *N*-Heteroaromatics



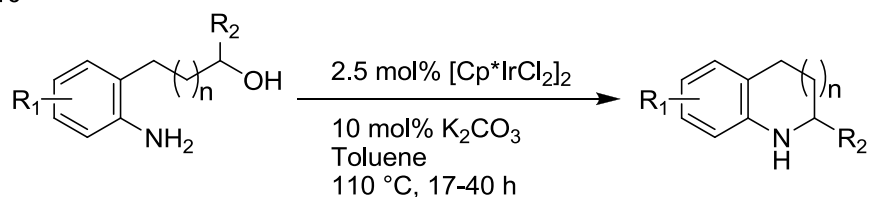
Scheme 5 - Selective Mono- or Di- Alkylation of Diols

Selectivity was also an issue with the amination of short chain diols. Work published by Marsella⁸ showed that under milder conditions than those used by Watanabe, it

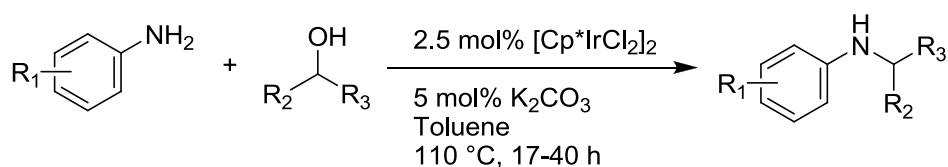
was possible to isolate 1,2-amino alcohols as the major products when using secondary amines (Scheme 5). However, this selectivity was reversed when $\text{RuCl}_3 \cdot x\text{H}_2\text{O}$ was used as the catalyst instead of $\text{RuCl}_2(\text{PPh}_3)_3$. Furthermore, he later showed that selectivity could be determined by sterics.⁹

After the initial reports it was almost 20 years before new catalysts appeared to improve and expand the scope of this type of C-N bond formation. Yamaguchi and Fujita were the first, demonstrating that $[\text{Cp}^*\text{IrCl}_2]_2$, in the presence of an activating base, was capable of cyclizing amino alcohols to form 1,2,3,4-tetrahydroquinolines¹⁰ (Scheme 6) under milder conditions (90-111 °C) than those reported by Watanabe. They were then able to demonstrate that this catalyst was not limited to intramolecular reactions, but could also be applied to intermolecular, examples alkylating anilines and other amines with a range of alcohols¹¹ successfully, as well as forming cyclic tertiary amines from primary amines and diols.¹²

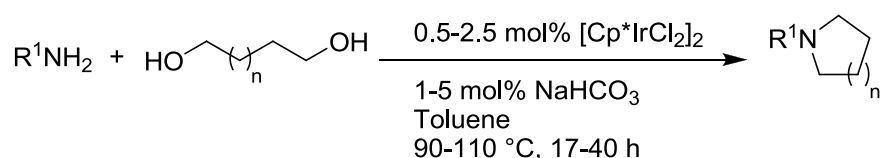
Ref 10



Ref 11

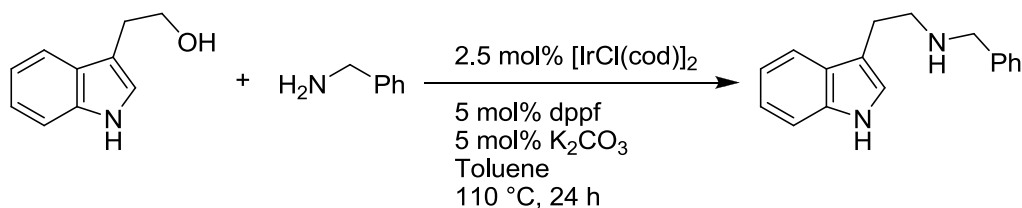


Ref 12



Scheme 6 - Iridium Catalysed C-N Bond Formation

Ref 13



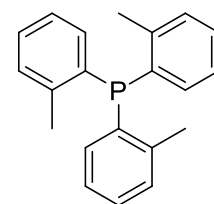
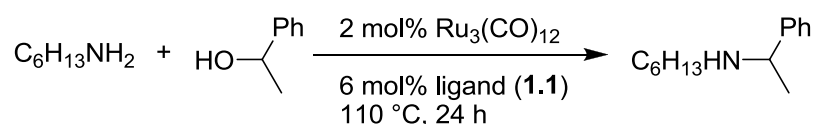
Scheme 13 - Alternative Iridium Based Catalyst

Williams and co-workers also demonstrated the use of an iridium based catalyst to effect C-N bond formation with a range of primary and secondary amines (Scheme 7).¹³

With the advances being made in iridium-catalysed C-N borrowing hydrogen, new ruthenium catalysts were not far behind with work published by Beller¹⁴ and Williams¹⁵ in quick succession.

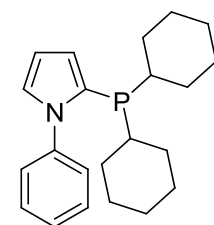
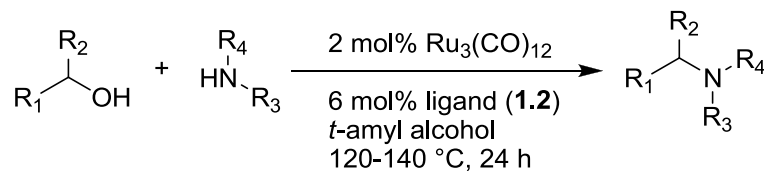
Beller and co-workers applied a ruthenium carbonyl cluster, $\text{Ru}_3(\text{CO})_{12}$, as a precatalyst with tri(*o*-tolyl)phosphine (**1.1**) added as the ligand. However, they found that the activity was significantly improved with the cataCXium[®] ligand¹⁶ (**1.2**) (Scheme 14). Both catalyst systems offer advantages over the previous work with this precatalyst.^{9,17} The modified catalyst was then applied to the synthesis of tertiary amines¹⁸ and selective mono-alkylation of vicinal diols,¹⁹ demonstrating both the scope and selectivity that the catalyst offered (Scheme 14).

Ref 16



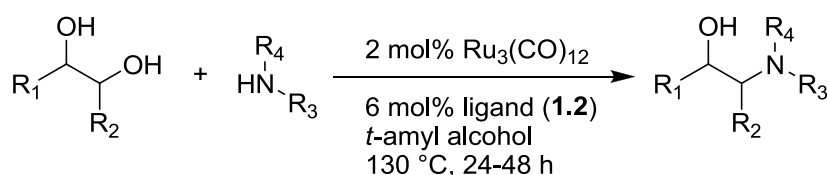
1.1

Ref 18



1.2

Ref 19

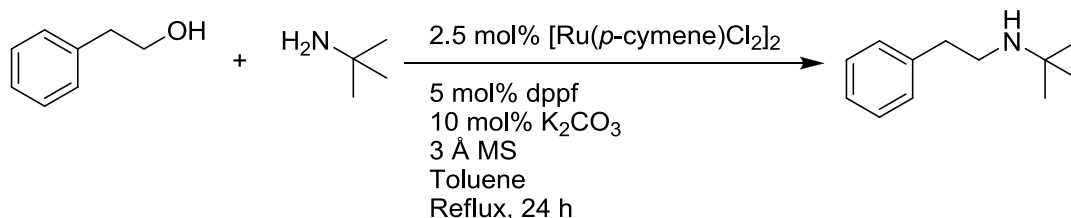


Scheme 14 - $\text{Ru}_3(\text{CO})_{12}$ Borrowing Hydrogen Reactions

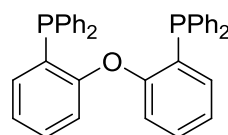
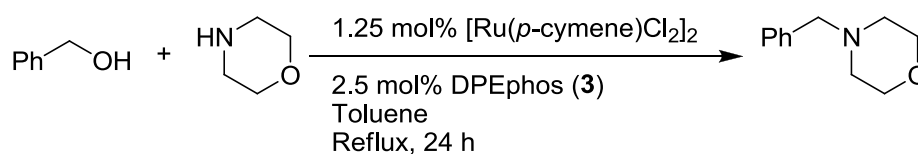
Williams and co-workers had also approached the problem in a similar fashion, screening ruthenium precatalysts for activity and then a series of phosphine ligands. They found that the combination of $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$ and a bidentate phosphine (dppf) in the presence of an activating base gave an active catalyst for the selective formation of secondary amines¹⁵ (Scheme 15). However, when applying this system to the synthesis of tertiary amines²⁰ the base was not necessary. Furthermore, they, like Beller found an alternative ligand, DPEphos (**1.3**) which led to increased catalyst

activity resulting in a lower catalyst loading. Later Williams was able to demonstrate that the activating base was not necessary for catalytic activity and had little effect on the isolated yield of the reaction.²¹

Ref 15



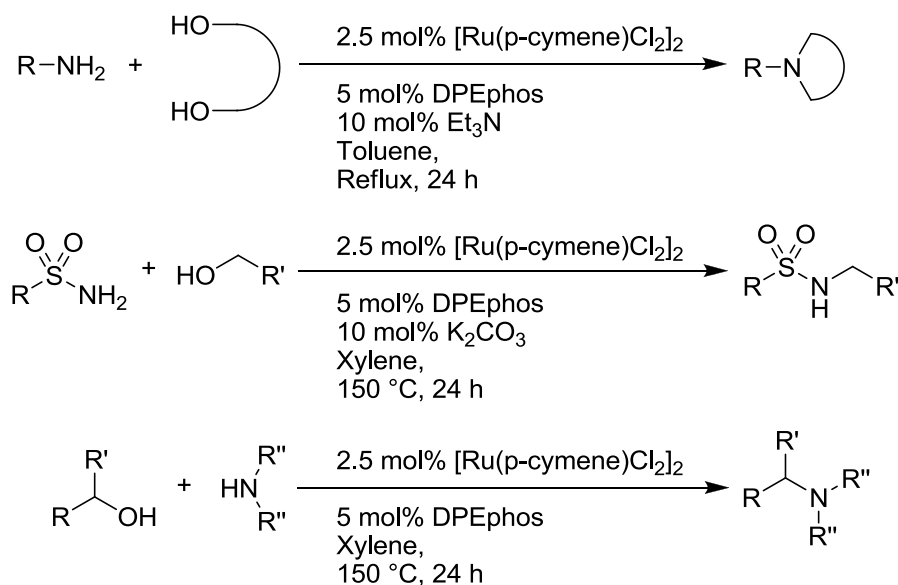
Ref 20



1.3

Scheme 15 - Initial Work by the Williams Group

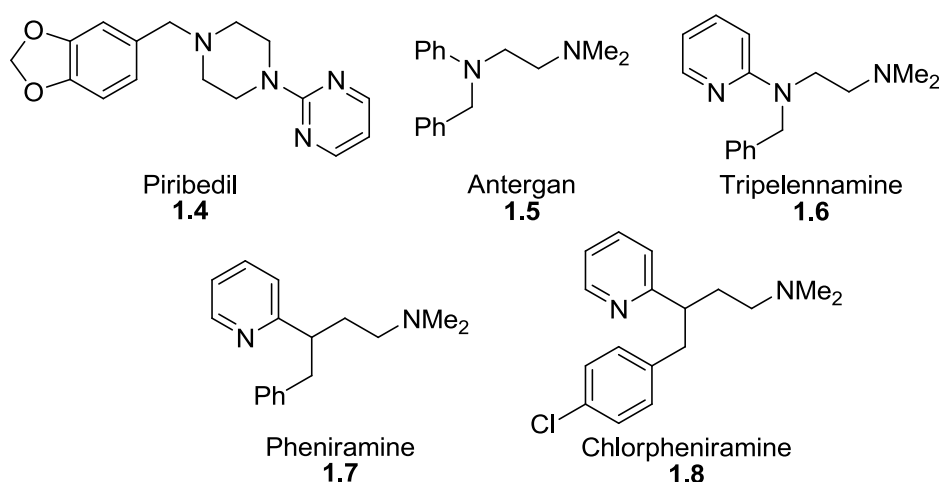
Ref 21



Scheme 16 - Ru/DPEphos Borrowing Hydrogen Reactions

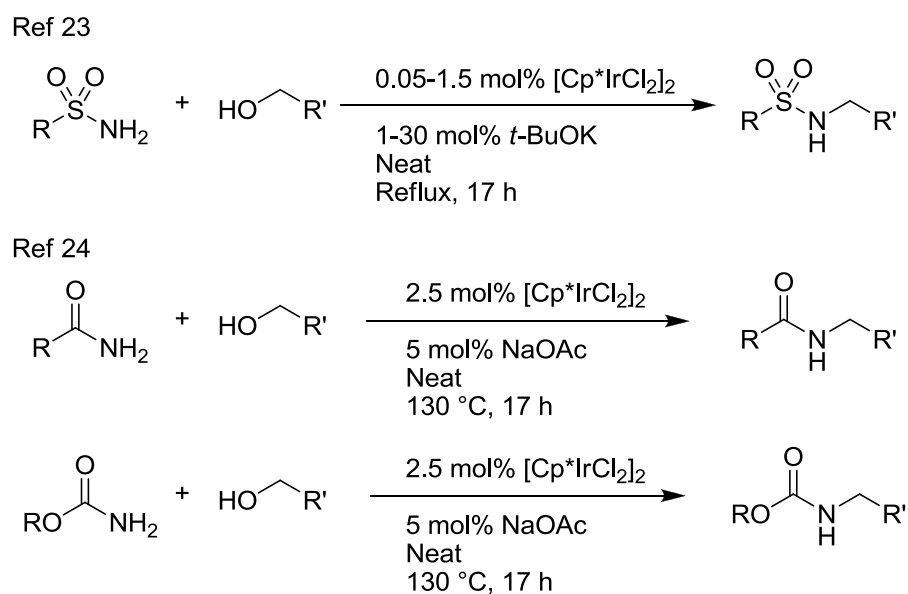
Indeed, the combination of [Ru(*p*-cymene)Cl₂]₂ and DPEphos has proven to be applicable to a wide range of C-N bond forming reactions including the coupling of

sulphonamides and secondary alcohols although at higher reaction temperatures (150 °C) (Scheme 16).²¹



Scheme 17 - Pharmaceutical Accessed *via* Borrowing Hydrogen

The utility of this methodology was also demonstrated by applying it successfully to the synthesis of several drug molecules, Piribedil (**1.4**), Antergan (**1.5**), Tripeleennamine (**1.6**), Pheniramine (**1.7**) and Chlorpheniramine (**1.8**) (Scheme 17).

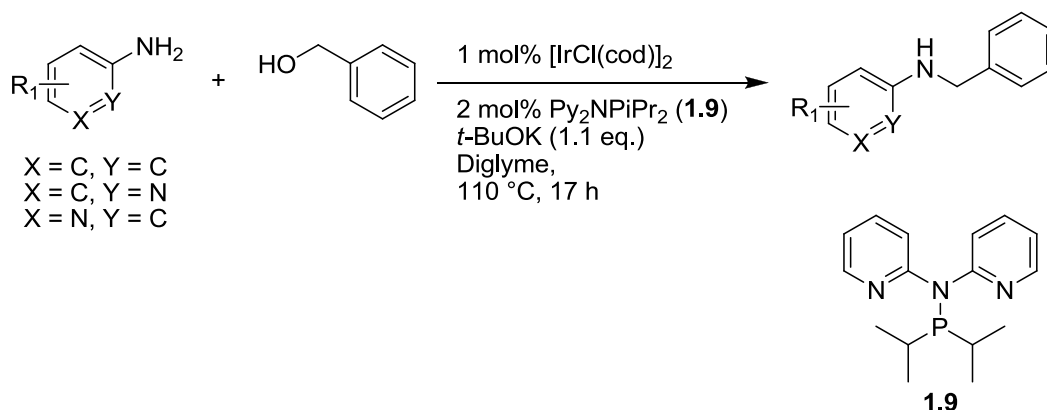


Scheme 18 - Expanded Scope of C-N Bond Formation with [Cp*IrCl₂]₂

Yamaguchi and co-workers were also able to expand the scope of their iridium catalyst system to the alkylation of secondary amines²² and sulphonamides²³ including the use of secondary alcohols, which had not been previously covered by Williams and co-workers. Furthermore, they successfully alkylated primary amides

and carbamates at milder temperatures²⁴ (130-140 °C) than previously reported by Watanabe³ or Jenner²⁵ (Scheme 18), although with some limitations on substrate scope.

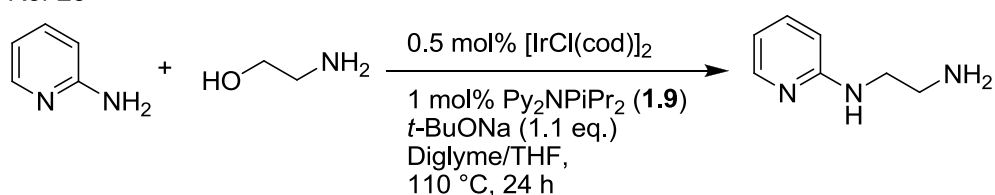
Ref 27



Scheme 19 - N-Alkylation of Heteroaromatic Amines Using a P-N Ligand

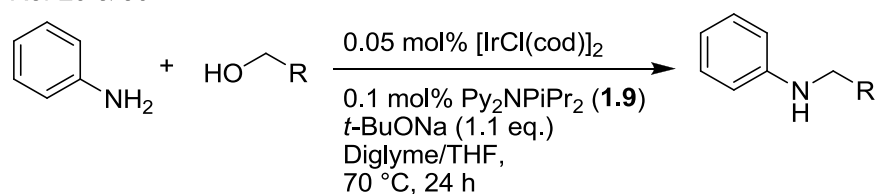
With Borrowing Hydrogen firmly established as a viable method, more interest and research into custom made ligands and catalysts to improve selectivity and reactivity followed. Building on earlier work by van Koten and co-workers,²⁶ Kempe and co-workers developed a series of P,N ligands²⁷ which when combined with an iridium precatalyst gave an active catalyst for the selective mono-alkylation of anilines and aminopyridines. Kempe went on to demonstrate that the catalyst was also active for the synthesis of diamines by monoalkylation of amino alcohols (Scheme 20).²⁸

Ref 28



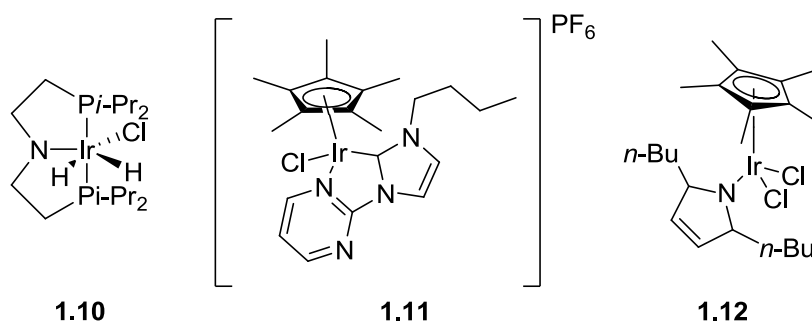
Scheme 20 - Synthesis of Diamines Using a P-N Ligand

Ref 29 & 30



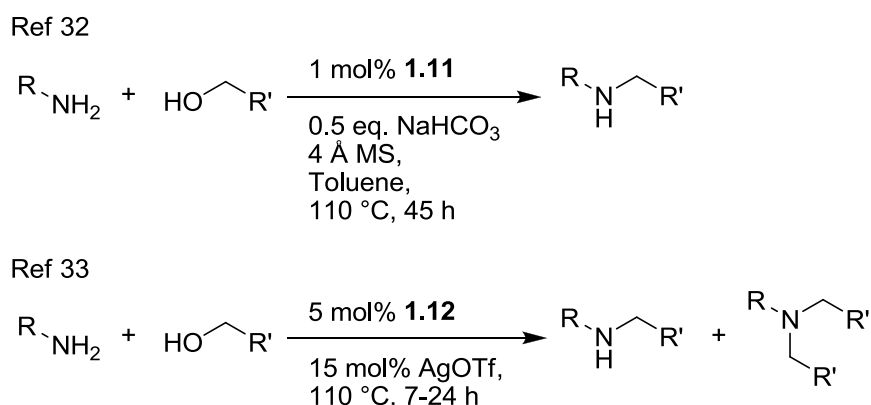
Scheme 21 - Low Temperature C-N Bond Formation *via* Borrowing Hydrogen

Kempe and co-workers were also able to show that their catalyst had advantages over the previous commercially available catalysts by performing C-N bond formation at 70 °C (Scheme 21).²⁹⁻³⁰ The disadvantage of their catalyst system, however, comes in the substrate scope. Whilst the catalyst is not deactivated by heteroaromatic amines or diamines, the reaction only works well for aromatic amines (anilines) with benzylic and aliphatic amines being reported to give poor results.²⁷



Scheme 22 - Carbene and Pincer Ligand Based Catalysts

Börner and co-workers³¹ also approached the design of new catalyst from the ligand, choosing to develop a pincer ligand in combination with $[\text{IrCl}(\text{coe})_2]_2$. This catalyst (**1.10**) has a wider substrate scope, being suitable for the coupling of aliphatic, benzylic and secondary amines; however, high reaction temperatures (120-140 °C) are required to achieve results similar to those obtained with the commercially available catalysts.

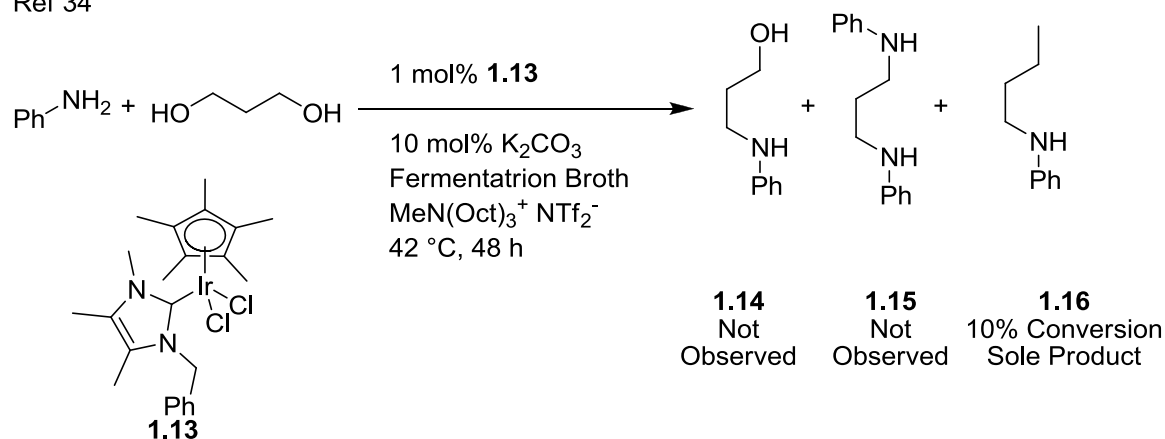


Scheme 23 - Carbene Based Catalysts for C-N Bond Formation via Borrowing Hydrogen Methodology

An alternative to pincer ligands has been the application of carbene ligands. These ligands have allowed the catalyst loadings of reactions to be lowered to ~1 mol% in most cases, but despite several articles describing a selection of catalysts, the

reactions either require longer reaction times (typically 48 h)³² or lack the selectivity of previous catalysts due to their increased reactivity (Scheme 23).³³

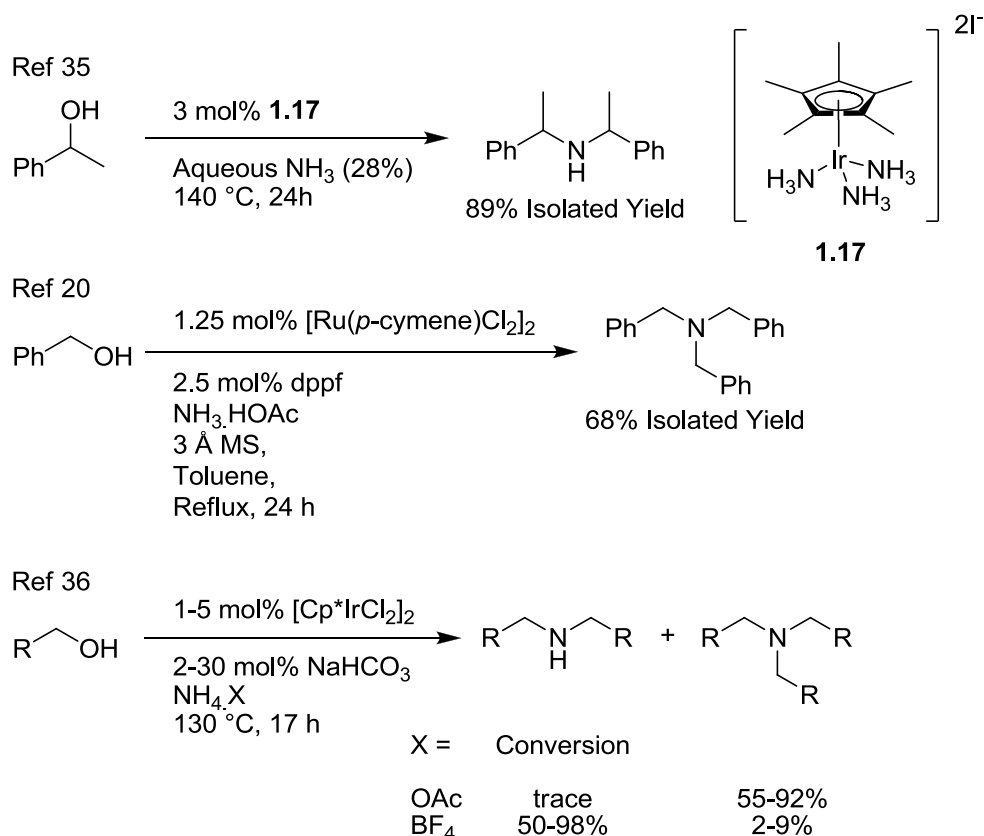
Ref 34



Scheme 24 - Work of Marr and Co-Workers

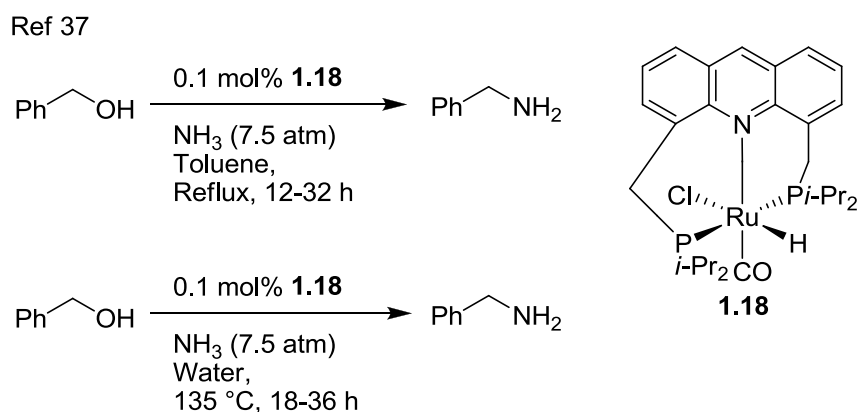
The use of carbene ligands whilst suffering from disadvantages, does offer increased catalyst stability. Marr and co-workers³⁴ found that this increased stability offered several advantages over previously reported systems. Their catalyst (**1.13**) could be used to effect selective mono-alkylation and dehydration of 1,3-propanediol to yield *N*-propylaniline (**1.16**) only, with the expected diamine (**1.15**) and amino alcohol (**1.14**) not being detected. This is a unique reaction not reported previously in the Borrowing Hydrogen literature. Furthermore, this reaction could be carried out at 42 °C in a biphasic mixture consisting of the an aqueous solution of the crude 1,3-propanediol (from a bacteria fermentation of glycerol) and an ionic liquid (methyl trioctyl ammonium bis triflimide). Whilst this stability and reactivity in terms of reaction temperature and product is unique, the low temperature meant that the reaction proceeded slowly, only generating a 10% conversion at 42 °C after 48 hours (Scheme 24).

The use of ammonia³⁵ and its salts^{20, 36} has resulted in the synthesis of tertiary amines, or secondary amines³⁶ by careful control of the stoichiometry or the acidity of the counter ion used in the salt. Even the use of sterically demanding secondary alcohols, leads to over alkylation and secondary amine formation (Scheme 25).³⁵ This is due to the increased nucleophilicity of the intermediate primary amine formed over the ammonia/ammonium salt used. This means that the second alkylation, from primary to secondary amine, is quicker than the first, and as a result the reaction is difficult to control.



Scheme 25 - The Use of Ammonia and Ammonium Salts in Borrowing Hydrogen

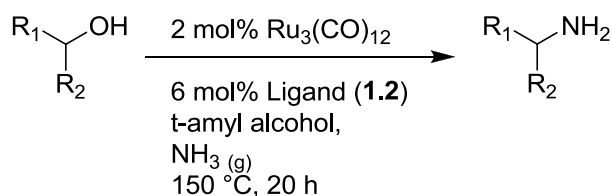
Primary amines can be selectively accessed by using a pressurised atmosphere of ammonia. Milstein and co-workers were the first to achieve this successfully using a preformed pincer ligand catalyst.³⁷ Milstein also found that the reaction could also be performed with water as the solvent (Scheme 26), although this is not the first example of water being used as a solvent in borrowing hydrogen reactions.^{35,38-40}



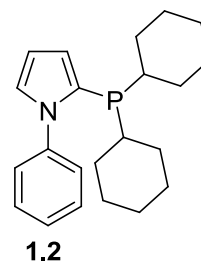
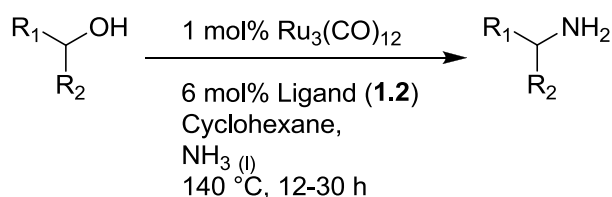
Scheme 26 - Milstein's Primary Amine Synthesis

More recently Beller⁴¹ and Vogt⁴² published, simultaneously, similar conditions for primary amine synthesis using the $\text{Ru}_3(\text{CO})_{12}$ /cataCXium[®] ligand (**2**) system although the reactions required elevated temperatures (140-150 °C) and were only applicable to secondary alcohols (Scheme 27).

Ref 41



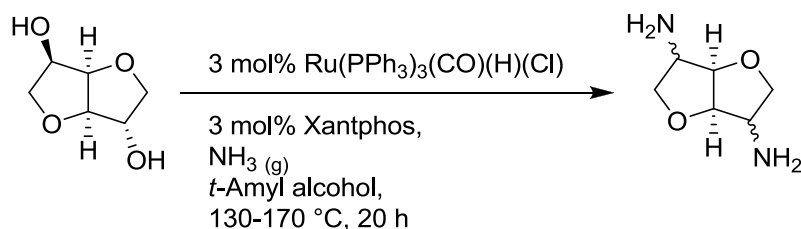
Ref 42



Scheme 27 - Beller and Vogt Primary Amine Syntheses

Beller and co-workers continued to work on this area and were successful again, finding an alternative ruthenium based catalyst system to access diamines from diols, where both amines were primary amines. The catalyst was also suitable for the synthesis of amino esters from hydroxy esters (Scheme 28). Comparison of this catalyst by Beller against the previously published system illustrated that this new system was superior, returning more than double the conversion and isolated yield of adamantamine under identical conditions.⁴³

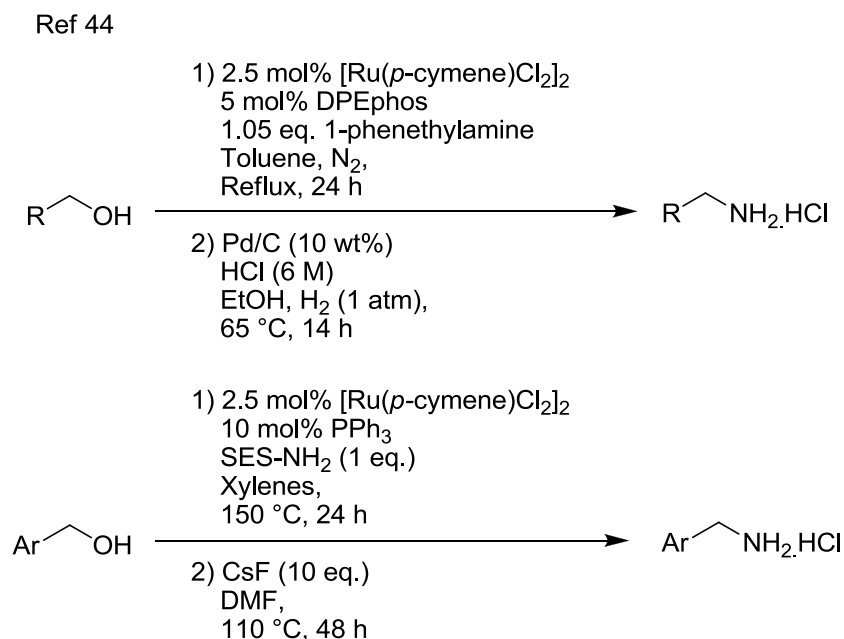
Ref 43



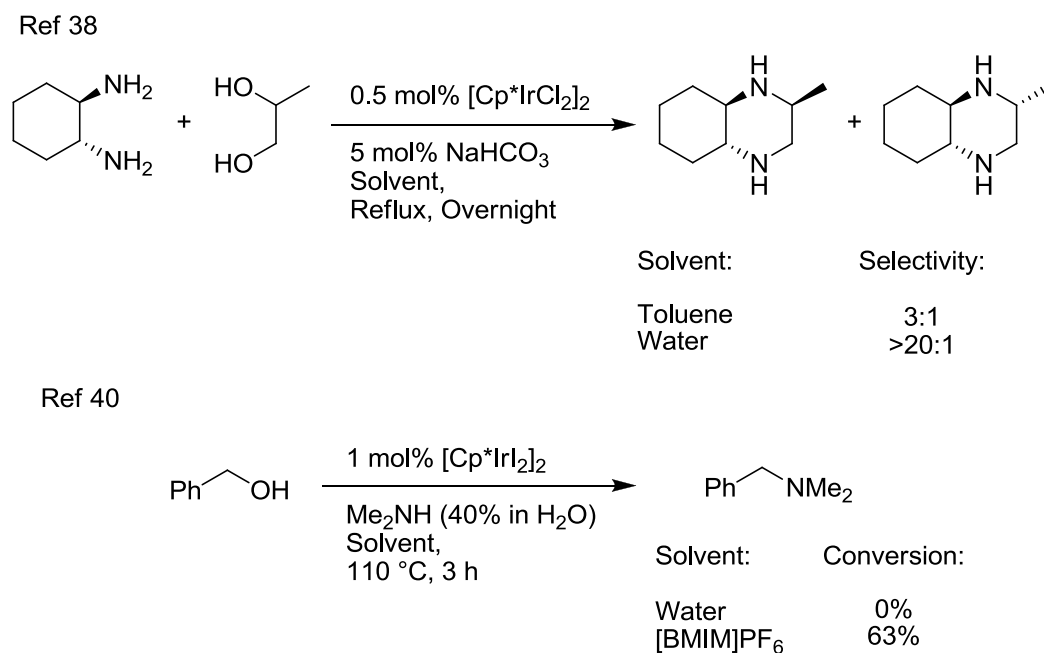
Scheme 28 - Primary Diamines From Diols

Williams and co-workers have also published a borrowing hydrogen based method to access primary amines. Accepting that under standard reaction conditions the use of ammonia and its salts led to over alkylation. They chose to approach the problem *via* masked ammonia sources such as benzylic amines and sulfonamides forming *N*-

protected secondary amines. The amines and amides could be selectively monoalkylated, avoiding the selectivity problems of using ammonia, before a second deprotection step revealed the primary amine. This process was possible with both benzylic amines and sulfonamides, and the deprotection could be performed *in-situ*, a one-pot two step synthesis (Scheme 29).⁴⁴



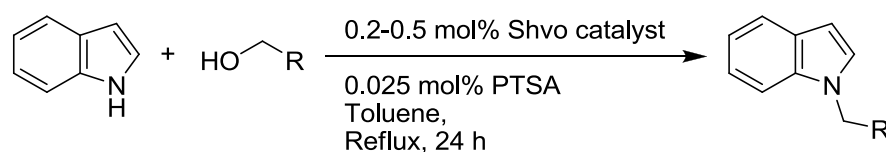
Scheme 29 - Primary Amines From via a Masked Amine Approach



Scheme 30 - Advantageous *N*-Alkylation In Water and Ionic Liquids

As mentioned above, Borrowing Hydrogen reactions are not solely limited to organic solvents such as toluene and xylene. Indeed both ionic liquids^{34,40} and water^{35,37-40} have successfully been used, often giving more advantageous results than toluene, either improved selectivity or yield. For examples; Madsen and co-workers use of $[\text{Cp}^*\text{IrCl}_2]_2$ to form piperazines from diols and diamines saw better diastereoselectivity in or on water³⁸ whilst Williams and co-workers saw faster reactions with secondary amines in ionic liquids than water (Scheme 30).⁴⁰

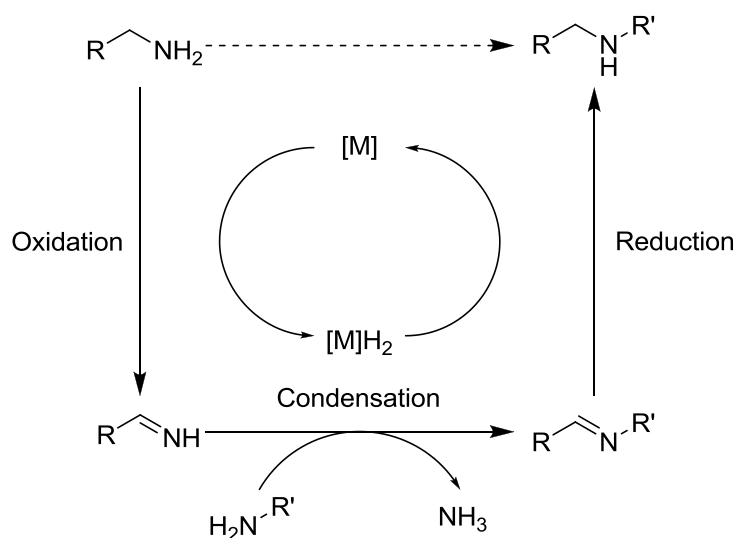
Ref 46



Scheme 31 - *N*-Alkylation of Indoles *via* Borrowing Hydrogen

Another relatively untapped area of C-N bond formation lies in the *N*-alkylation of nitrogen containing heteroaromatic compounds. Two reports are present in the literature; the first by Watanabe⁴⁵ uses harsh conditions (200 °C) but has a wide substrate tolerance. However, more recently a joint effort by Williams and Beller⁴⁶ was able to affect *N*-alkylation of indole under conditions more consistent with current borrowing hydrogen methodologies (Scheme 31).

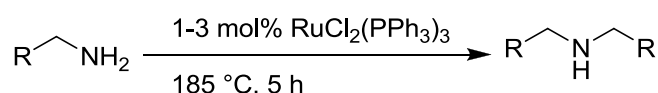
Borrowing Hydrogen hasn't been limited to using alcohols as alkylating agents, amines can also be used eliminating ammonia as the byproduct instead of water (Scheme 32).



Scheme 32 - Alkylation of Amines with Amines *via* Borrowing Hydrogen

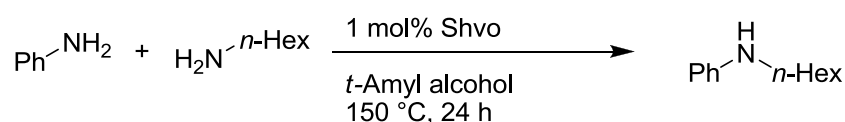
The condensation of benzylamine to dibenzylamine is well known, however, selective alkylation of other amines is less well known. The first example in the literature of this reaction using borrowing hydrogen detailed the self-condensation of a variety of amines selectively to the corresponding secondary amine using $\text{RuCl}_2(\text{PPh}_3)_3$ (Scheme 33).⁴⁷

Ref 47

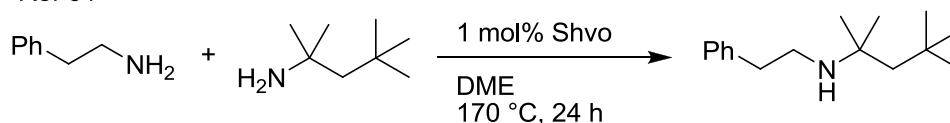
**Scheme 33 - Selective Amine Condensation**

This first example only illustrated that self-condensation of amines was possible. Another example, also using harsh conditions (180 °C) showed some progress, selectively coupling anilines and tetra-substituted ammonium salts in the presence of tin chloride.⁴⁸ However, Beller and co-workers have had success in the selective cross coupling of amines. By applying Shvo's catalyst and amines such as anilines⁴⁹⁻⁵⁰ and amines with an adjacent tertiary centre⁵¹ the group were able to selectively alkylate with a variety of coupling amines. The amines that could be oxidised and used as alkylating agents include; primary amines, symmetric secondary and tertiary amines as well as cyclic secondary amines (Scheme 34).⁵²

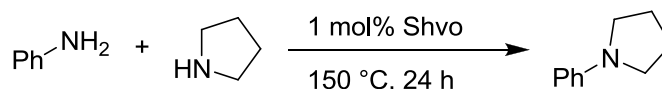
Ref 49 & 50



Ref 51



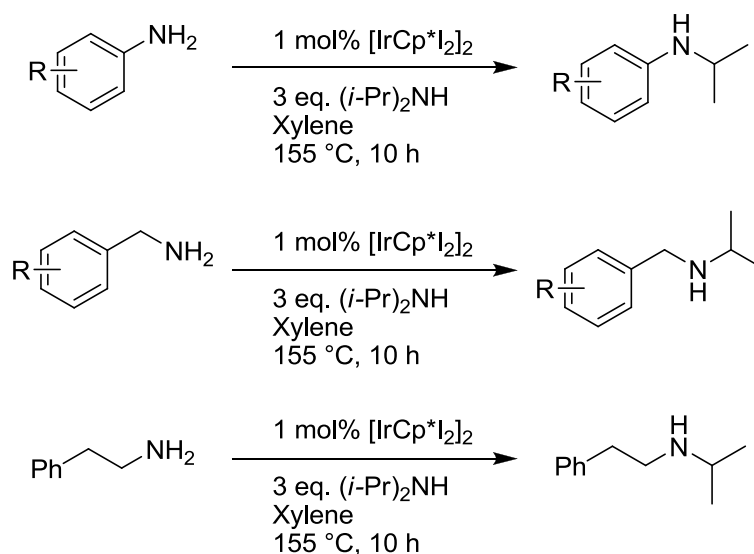
Ref 52

**Scheme 34 - Selective Cross Coupling of Amines by Beller and Co-Workers**

Williams and co-workers were more successful, obtaining selectivity without the use of tertiary centres. Using $[\text{Cp}^*\text{IrI}_2]_2$ that had previously been shown to racemize chiral secondary amines,⁵³⁻⁵⁴ the group were able to selectively alkylate anilines, benzylic

amines and primary alkylamines using diisopropyl and other amines with secondary α -centres in good yields (Scheme 35).⁵⁵

Ref 55

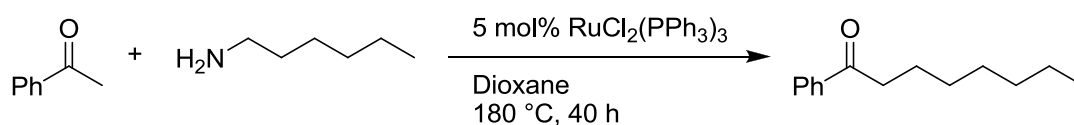


Scheme 35 - Selective Amine Cross Coupling By Williams and Co-Workers

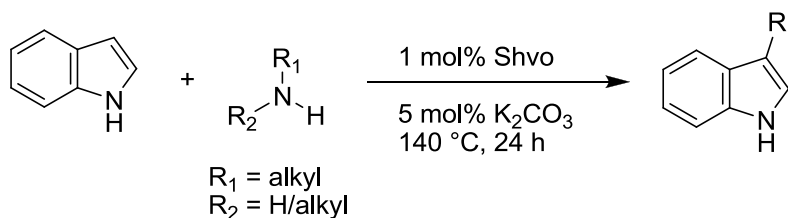
Madsen and co-workers also published a similar article using $[\text{IrCp}^*\text{Cl}_2]_2$ however, only forming self-condensed secondary amines.⁵⁶

1.2 C-C Bond Forming Borrowing Hydrogen Reactions

Ref 57



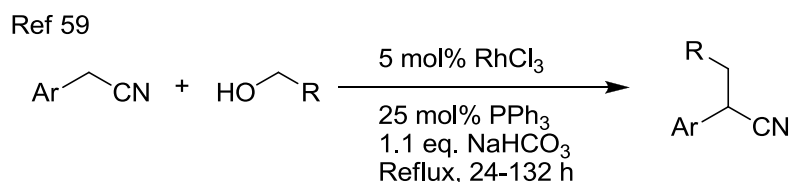
Ref 58



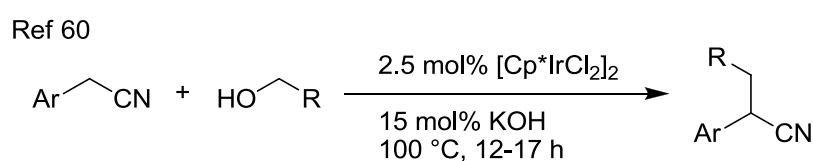
Scheme 36 - Alkylation of Carbon Nucleophiles with Amines

Amines aren't solely limited to amine-amine cross couplings, similarly to alcohols, they can be used as alkylating agents for carbon nucleophiles such as ketones⁵⁷ and indoles (Scheme 36).⁵⁸

The alkylation of carbon nucleophiles with alcohols is well known, with many examples in the literature. The first published work was by Grigg and co-workers using a rhodium catalyst in the presence of a base to alkylate benzylic nitriles (Scheme 37).⁵⁹

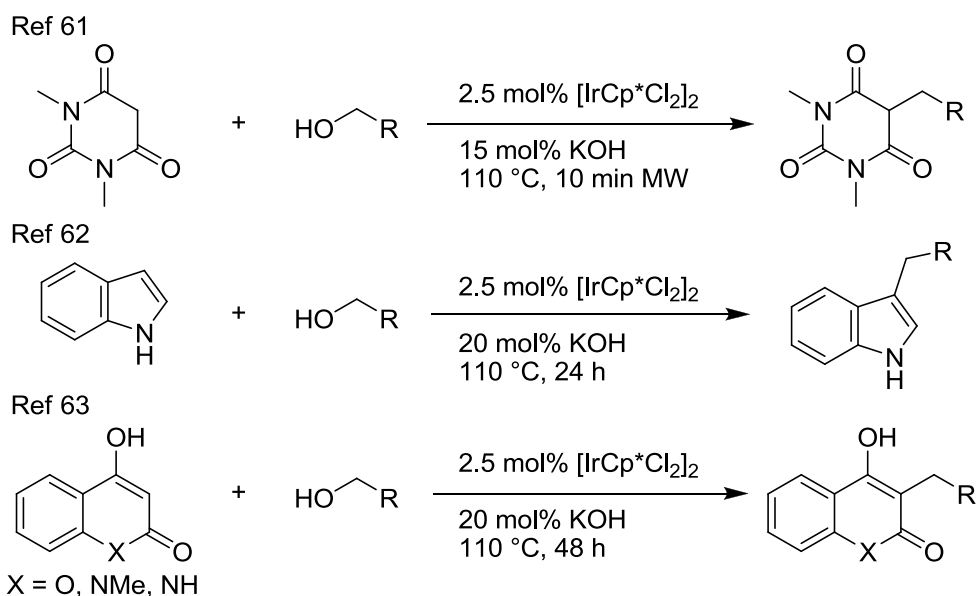


Scheme 37 - Alkylation of Benzylic Nitriles with Alcohols



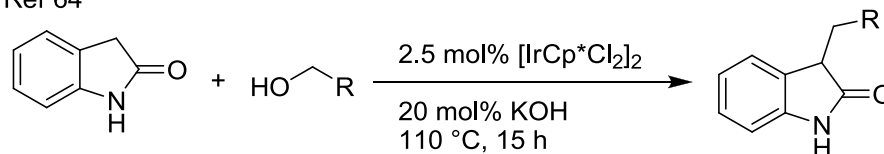
Scheme 38 - Alkylation of Benzylic Nitriles with an Iridium Catalyst

Grigg later revisited this work, applying the $[\text{Cp}^*\text{IrCl}_2]_2$ catalyst used by Yamaguchi and Fujita to effect a more efficient system, reducing the reaction times to less than 18 hours (Scheme 38).⁶⁰ Grigg and co-workers were then able to apply the $[\text{IrCp}^*\text{Cl}_2]_2$ to the alkylation of a wide range of nucleophiles including; 1,3-dimethylbarbituric acid,⁶¹ C3-alkylation of indoles,⁶² 4-hydroxycoumarins and 4-hydroxy-2-quinolones (Scheme 39).⁶³

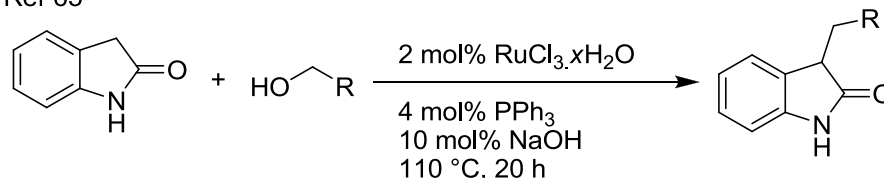


Scheme 39 - Alkylation of Nucleophiles with Alcohols

Ref 64

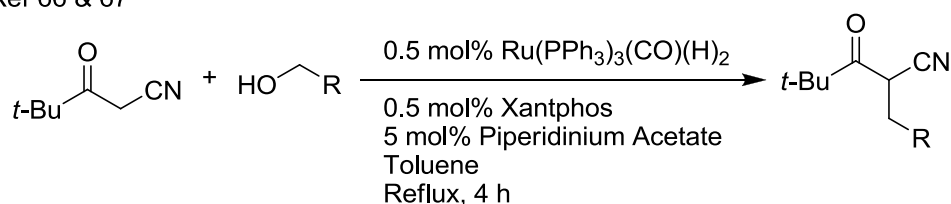


Ref 65

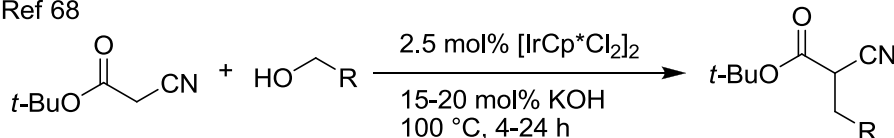
**Scheme 40 - Alkylation of Oxindole**

The alkylation of oxindoles was reported by Grigg⁶⁴ and Madsen⁶⁵ within weeks of each other. Despite the differences in the metal catalyst, the reports gave very similar results and Madsen highlighted the $[\text{Cp}^*\text{IrCl}_2]_2$ catalyst used by Grigg in his initial catalyst screen, discarding it in favour of a cheaper ruthenium-based catalyst (Scheme 40).

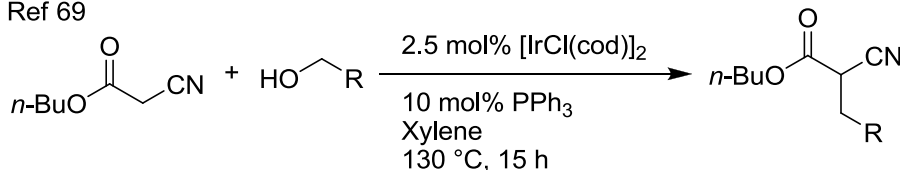
Ref 66 & 67



Ref 68

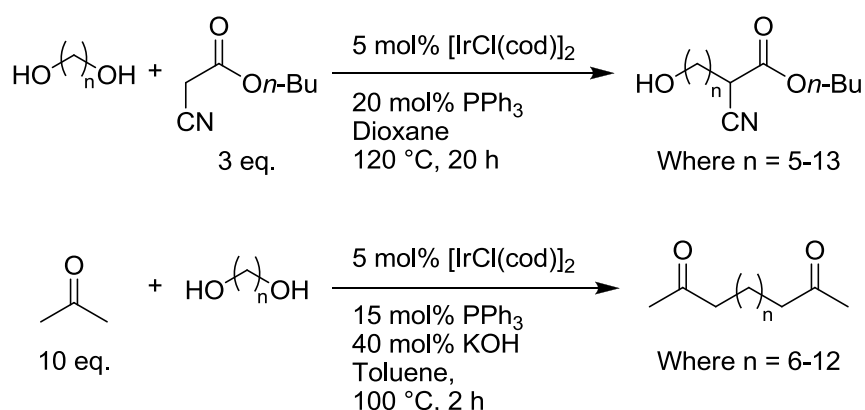


Ref 69

**Scheme 41 - Alkylation of Activated Nitriles**

Other C-C bond forming alkylations include a selection of similarly activated nitriles which have been reported by Williams using $\text{Ru}(\text{PPh}_3)_3(\text{CO})(\text{H})_2$,⁶⁶⁻⁶⁷ and Grigg⁶⁸ and Ishii⁶⁹ both using iridium based catalysts (Scheme 41).

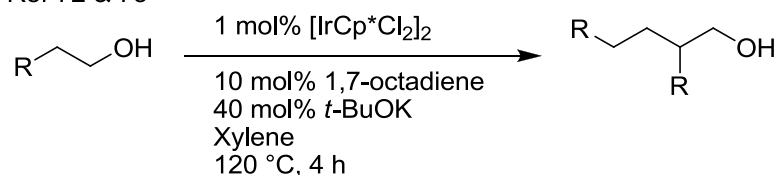
Ref 71



Scheme 42 - Selective Mono- and Di-Alkylation of Diols

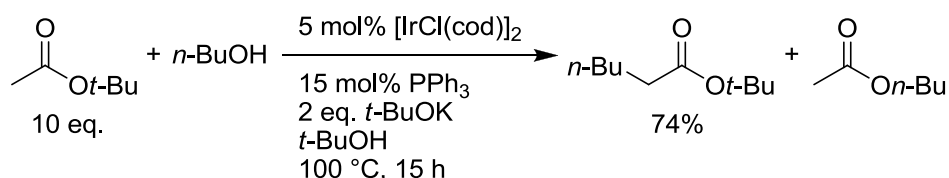
Interestingly, in his report, Ishii demonstrated that a diol could be di-alkylated. The dialkylation of ketones with alcohols had been previously reported by Ishii,⁷⁰ however, further work by Ishii demonstrated that mono- or di-alkylation of diols⁷¹ could be achieved selectively by simple control of the stoichiometry (Scheme 42).

Ref 72 & 73



Scheme 43 - Self Condensation of Alcohols

Ishii and co-workers have been very active, developing several C-C bond forming borrowing hydrogen reactions. By generating the enolate formed from the aldehyde, Ishii was able to show that the alcohol could also be used as a nucleophile to react with itself, forming β -alkylated products from the self-condensation of alcohols (Scheme 43).⁷²⁻⁷³

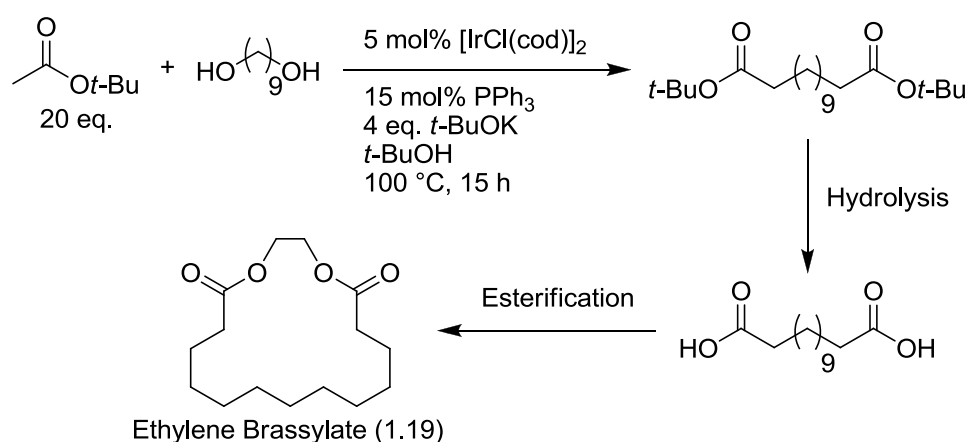


Scheme 44 - α -Alkylation of Acetates

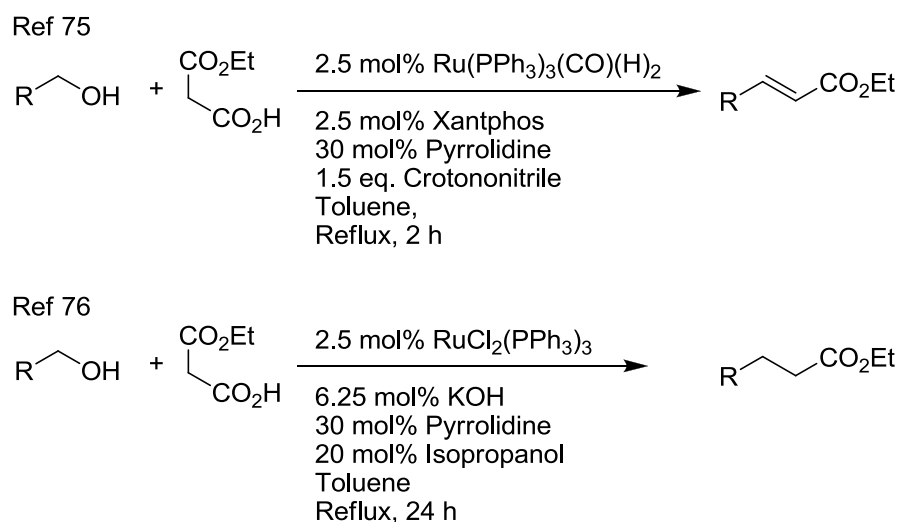
However, one of Ishii's most interesting pieces of work focused on the α -alkylation of acetates, more importantly, avoiding trans-esterification by using a large excess of

the acetate (Scheme 44).⁷⁴ Again, it was possible to di-alkylate diols, the product of which was hydrolysed and then esterified with ethylene glycol to form ethylene brassylate (**1.19**) a fragrance compound (Musk T) (Scheme 45).

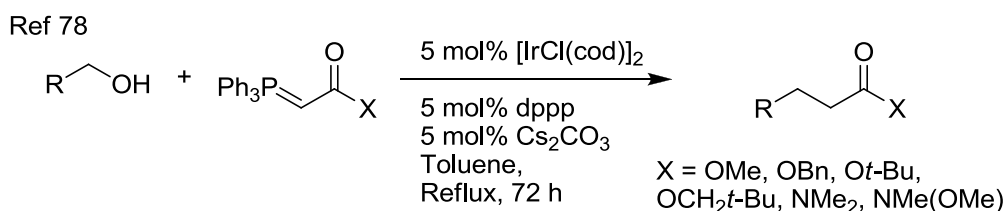
Williams and co-workers have also looked at the alkylation of esters in the form of malonate half esters. Their first attempt suffered from dehydrogenation resulting in a mixture of reduced alkylated ester and the α,β -unsaturated ester. This was overcome, however, by the use of crotononitrile as an oxidant, isolating only the α,β -unsaturated esters (Scheme 46).⁷⁵ Further work screening catalysts led to a more suitable catalyst system including the addition of isopropanol, allowing access to the reduced ester as well (Scheme 46).⁷⁶



Scheme 45 - Application of Acetate Alkylation

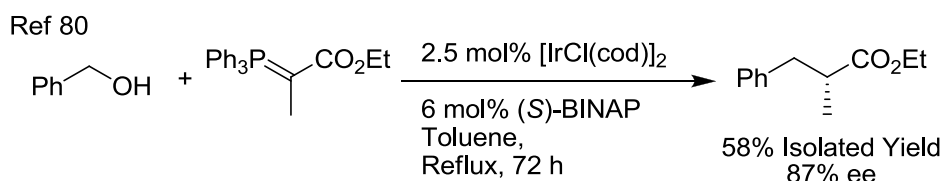


Scheme 46 - Applications of Malonate Esters in Borrowing Hydrogen & Hydrogen Transfer Methodologies



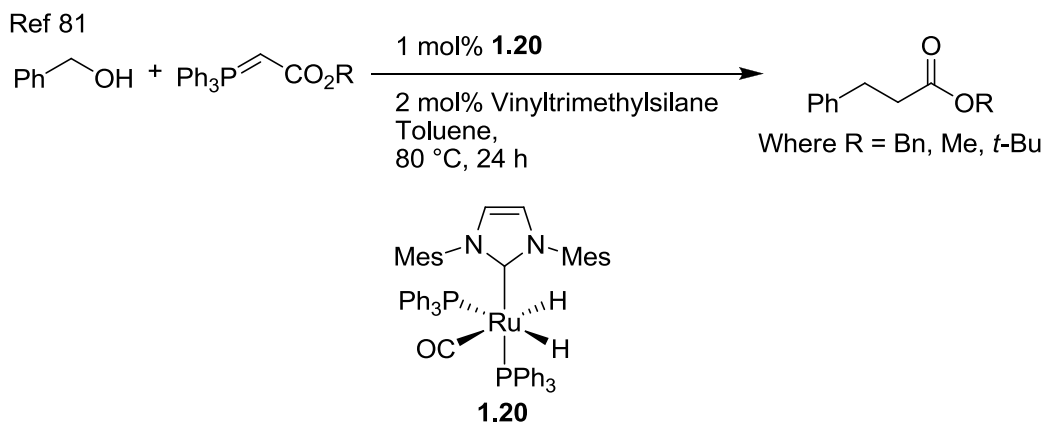
Scheme 47 - Wittig Reagents in Borrowing Hydrogen

Williams and co-workers have also published work on iridium based C-C bond formation using Wittig reagents (Scheme 47).⁷⁷⁻⁷⁹



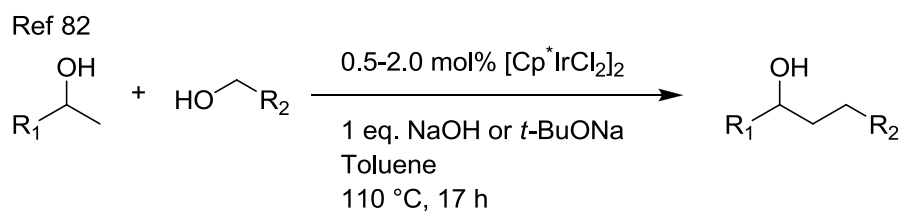
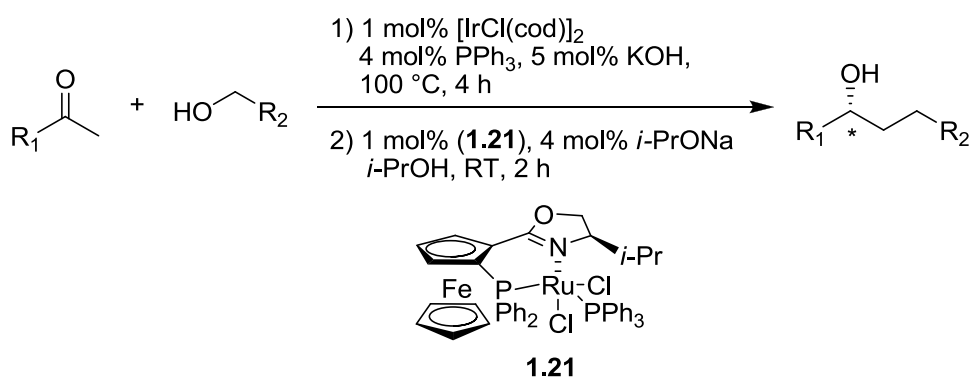
Scheme 48 - Asymmetric Borrowing Hydrogen Methodology

Furthermore they were able to develop an asymmetric variant,⁸⁰ which is the first application of borrowing hydrogen methodology in asymmetric synthesis (Scheme 48). However, more recent joint efforts from Williams and Whittlesey have shown that the combination of the commercially available Ru(PPh₃)₃(CO)(H)₂ with carbenes produces very active catalysts for C-C bond formation (Scheme 49).⁸¹

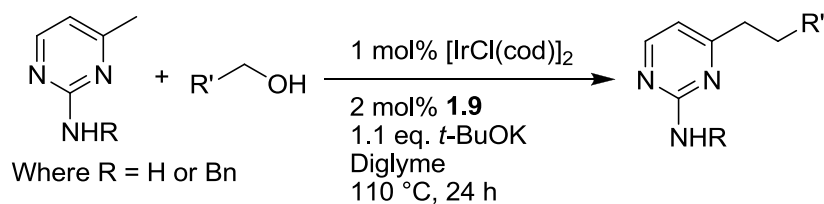


Scheme 49 - Ruthenium Carbene Catalyst for C-C Bond Formation

Yamaguchi and Fujita have also published work on C-C bond formation as well as the C-N work mentioned previously. They reported the use of their [Cp*IrCl₂]₂ catalyst for the alkylation of secondary alcohols (Scheme 50).⁸²

**Scheme 50 - Alkylation of Secondary Alcohols****Scheme 51 - Two Step, One Pot Access to β -Alkylated Chiral Alcohols from Ketones**

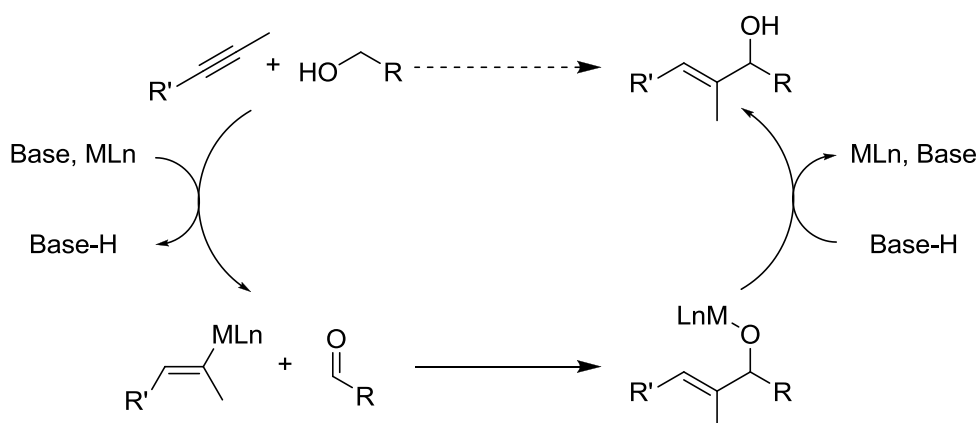
Whilst there has been some work on the β -alkylation of alcohols,^{32-33,82-83} there has been a significant amount of research and publication on the related β -alkylation of ketones.^{70-71,84-87} An interesting variation was published by Nishibayashi, where the alkylated ketone was then reduced in a two-step sequence, using asymmetric transfer hydrogenation to access the chiral alcohol (Scheme 51).⁸⁸

**Scheme 52 - Methyl Activation Towards Borrowing Hydrogen**

Almost all the major contributors to the Borrowing Hydrogen literature have published work on both C-N and C-C bond formation, and Kempe is no exception. Whilst *N*-alkylating a pyrimidine with a methyl group ortho to a nitrogen, they also noticed alkylation of the methyl group well as the expected *N*-alkylation.⁸⁹ Investigation showed that C-alkylation still occurred if the nitrogen was benzyl protected, although an excess of alcohol was required to drive both *N*- and C-alkylation to completion. Further screening demonstrated that this reaction was not

reliant on the nitrogen atom directing the alkylation, as seen with some C-H activation⁹⁰ as 4-methyl pyridine could also be alkylated, although with a lower yield (45%). Considering this result, the authors assumed the reaction to be dictated by the electronics of the aromatic ring which was proved by the use of 3-methylpyridine which saw no alkylation whatsoever.

Krische and his group also work in the area of C-C bond forming Borrowing Hydrogen, although the mode of action they apply is very different to previous work that has been discussed in this chapter. Interested in crotylations and allylations avoiding the use stoichiometric metals, the group found that rhodium and iridium catalysts in the presence of a hydrogen atmosphere would catalyse the addition of alkynes to aldehydes,⁹¹ ketones⁹² and imines.⁹³ Later work demonstrated that isopropanol could be used as an alternative hydrogen source,⁹⁴ which led on to the finding that in fact the corresponding alcohol could be used instead of the aldehyde without the need for a hydrogen source. A mechanism is shown below to illustrate how these reactions are believed to occur (Scheme 53).



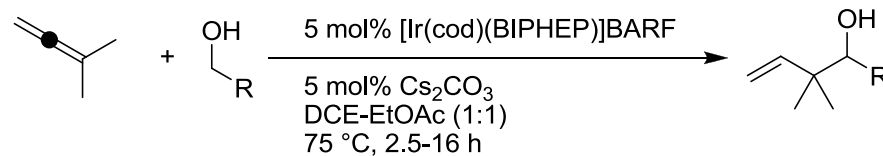
Scheme 53 - Krische Approach To Borrowing Hydrogen

The first step involves base-mediated oxidation of the alcohol to the corresponding aldehyde, generating a metal hydride. The metal hydride then adds across the alkyne to form an organo-metallic species that then adds directly to the aldehyde. Protonation then releases the metal catalyst to repeat the cycle whilst forming the product.

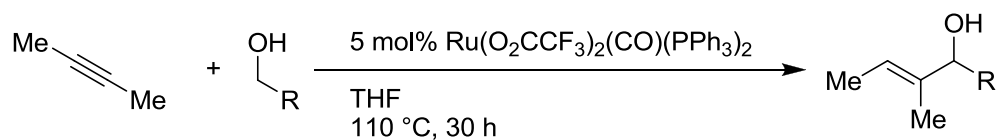
Krische and co-workers have expanded on their original work based on allenes⁹⁴ illustrating that a wide variety of allenes,⁹⁴⁻⁹⁶ alkynes,⁹⁷⁻⁹⁸ dienes,⁹⁹⁻¹⁰¹ enynes¹⁰² and activated alkenes¹⁰³ can be used with a range of different iridium and ruthenium based catalysts (Scheme 54). What is really unique about the work of Krische and co-

workers, is the tolerance of double bonds. Previous borrowing hydrogen work has seen partial or full reduction of double bonds, but this is not observed with Krische's system.

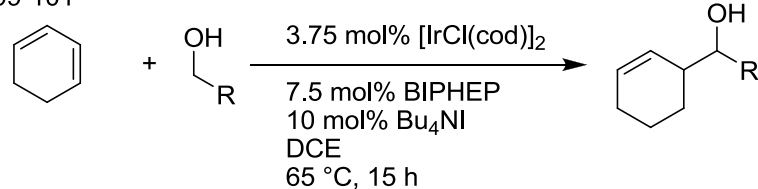
Ref 94-96



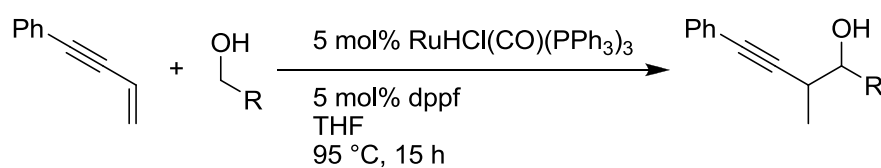
Ref 97-98



Ref 99-101



Ref 102



Scheme 54 -Range of Krische Style Borrowing Hydrogen Reactions

To conclude, Borrowing Hydrogen has advanced considerably since the first publications, particularly over the past 10-15 years. While it is still an expanding area, research must focus on new catalysts which are able to run at lower temperatures with wide substrate scope.

1.3 Reference

- [1] Grigg, R.; Mitchell, T. R. B.; Sutthivaiyakit, S.; Tongpenyai, N. *J. Chem. Soc. Chem. Commun.* **1981**, 611.
- [2] Watanabe, Y.; Tsuji, Y.; Ohsugi, Y. *Tetrahedron Lett.* **1981**, 22, 2667-2670.
- [3] Murahashi, S.-I.; Kondo, K.; Hakata, T. *Tetrahedron Lett.* **1982**, 23, 229-232.
- [4] Watanabe, Y.; Ohta, T.; Tsuji, Y. *Bull. Chem. Soc. Jpn.* **1983**, 56, 2647-2651.
- [5] Tsuji, Y.; Huh, K.-T.; Ohsugi, Y.; Watanabe, Y. *J. Org. Chem.* **1985**, 50, 1365-1370.
- [6] Watanabe, Y.; Tsuji, Y.; Ige, H.; Ohsugi, Y.; Ohta, T. *J. Org. Chem.* **1984**, 49, 3359-3363.
- [7] Watanabe, Y.; Morisaki, Y.; Kondo, T.; Mitsudo, T. *J. Org. Chem.* **1996**, 61, 4214-4218.
- [8] Marsella, J. A. *J. Org. Chem.* **1987**, 52, 467-468.
- [9] Marsella, J. A. *J. Organomet. Chem.* **1991**, 407, 97-105.
- [10] Fujita, K.; Yamamoto, K.; Yamaguchi, R. *Org. Lett.* **2002**, 4, 2691-2694.
- [11] Fujita, K.; Li, Z.; Ozeki, N.; Yamaguchi, R. *Tetrahedron Lett.* **2003**, 44, 2687-2690.
- [12] Fujita, K.; Fujii, T.; Yamaguchi, R. *Org. Lett.* **2004**, 6, 3525-3528.
- [13] Cami-Kobeci, G.; Slatford, P. A.; Whittlesey, M. K.; Williams, J. M. J. *Bioorg. Med. Chem. Lett.* **2005**, 15, 535-537.
- [14] Tillack, A.; Hollmann, D.; Michalik, D.; Beller, M. *Tetrahedron Lett.* **2006**, 47, 8881-8885.
- [15] Hamid, M. H. S. A.; Williams, J. M. J. *Chem. Commun.* **2007**, 725-727.
- [16] Hollmann, D.; Tillack, A.; Michalik, D.; Jackstell, R.; Beller, M. *Chem. Asian. J.* **2007**, 2, 403-410.
- [17] Jenner, G.; Bitsi, G. *J. Mol. Catal.* **1988**, 45, 165-168.

- [18] Tillack, A.; Hollmann, D.; Mevius, K.; Michalik, D.; Bähn, S.; Beller, M. *Eur. J. Org. Chem.* **2008**, 4745-4750.
- [19] Bähn, S.; Tillack, A.; Imm, S.; Mevius, K.; Michalik, D.; Hollmann, D.; Neubert, L.; Beller, M. *ChemSusChem*, **2009**, 2, 551-557.
- [20] Hamid, M. H. S. A.; Williams, J. M. J. *Tetrahedron Lett.* **2007**, 48, 8263-8265.
- [21] Hamid, M. H. S. A.; Allen, C. L.; Lamb, G. W.; Maxwell, A. C.; Maytum, H. C.; Watson, A. J. A.; Williams, J. M. J. *J. Am. Chem. Soc.* **2009**, 131, 1766-1774.
- [22] Fujita, K.; Enoki, Y.; Yamaguchi, R. *Tetrahedron*, **2008**, 64, 1943-1954
- [23] Zhu, M.; Fujita, K.; Yamaguchi, R. *Org. Lett.* **2010**, 12, 1336-1339.
- [24] Fujita, K.; Komatsubara, A.; Yamaguchi, R. *Tetrahedron*, **2009**, 65, 3624-3628.
- [25] Jenner, G. *J. Mol. Catal.* **1989**, 55, 241-246.
- [26] Abbenhuis, R. A. T. M.; Boersma, J.; van Koten, G. *J. Org. Chem.* **1998**, 63, 4282-4290.
- [27] Blank, B.; Madalska, M.; Kempe, R. *Adv. Synth. Catal.* **2008**, 350, 749-758.
- [28] Blank, B.; Michlik, S.; Kempe, R. *Adv. Synth. Catal.* **2009**, 351, 2903-2911.
- [29] Blank, B.; Michlik, S.; Kempe, R. *Chem. Eur. J.* **2009**, 15, 3790-3799.
- [30] Michlik, S.; Kempe, R. *Chem. Eur. J.* **2010**, 16, 13193-13198.
- [31] Andrushko, N.; Andrushko, V.; Roose, P.; Moonen, K.; Börner, A. *ChemCatChem*, **2010**, 2, 640-643.
- [32] Gnanamgari, D.; Sauer, E. L. O.; Schley, N. D.; Butler, C.; Incarvito, C. D.; Crabtree, R. H. *Organometallics*, **2009**, 28, 321-325.
- [33] Prades, A.; Corberán, R.; Poyatos, M.; Peris, E. *Chem. Eur. J.* **2008**, 14, 11474-11479.
- [34] Liu, S.; Rebros, M.; Stephens, G.; Marr, A. C. *Chem. Commun.* **2009**, 2308-2310.

- [35] Kawahara, R.; Fujita, K.; Yamaguchi, R. *J. Am. Chem. Soc.* **2010**, *132*, 15108-15111.
- [36] Yamaguchi, R.; Kawagoe, S.; Asai, C.; Fujita, K. *Org. Lett.* **2008**, *10*, 181-184.
- [37] Gunanathan, C.; Milstein, D. *Angew. Chem. Int. Ed.* **2008**, *47*, 8661-8664.
- [38] Nordstrøm, L. U.; Madsen, R. *Chem. Commun.* **2007**, 5034-5036.
- [39] Saidi, O.; Blacker, A. J.; Farah, M. M.; Marsden, S. P.; Williams, J. M. J. *Chem. Commun.* **2010**, 1541-1543.
- [40] Saidi, O.; Blacker, A. J.; Lamb, G. W.; Marsden, S. P.; Taylor, J. E.; Williams, J. M. J. *Org. Process Res. Dev.* **2010**, *14*, 1046-1049.
- [41] Imm, S.; Bähn, S.; Neubert, L.; Neumann, H.; Beller, M. *Angew. Chem. Int. Ed.* **2010**, *49*, 8126-8129.
- [42] Pinggen, D.; Müller, C.; Vogt, D. *Angew. Chem. Int. Ed.* **2010**, *49*, 8130-8133,
- [43] Imm, S.; Bähn, S.; Zhang, M.; Neubert, L.; Neumann, H.; Klasovsky, F.; Pfeffer, J.; Haas, T.; Beller, M. *Angew. Chem. Int. Ed.* **2011**, *50*, 7599-7603.
- [44] Lamb, G. W.; Watson, A. J. A.; Jolley, K. E.; Maxwell, a. C.; Williams, J. M. J. *Tetrahedron Lett.* **2009**, *50*, 3374-3377.
- [45] Tanaka, N.; Hatanaka, M.; Watanabe, Y. *Chem. Lett.* **1992**, *4*, 575-578.
- [46] Bähn, S.; Imm, S.; Mevius, K.; Neubert, L.; Tillack, A.; Williams, J. M. J.; Beller, M. *Chem. Eur. J.* **2010**, *16*, 3590-3593.
- [47] Bui-The-Khai; Concilio, C.; Porzi, G. *J. Organomet. Chem.* **1981**, *208*, 249-251.
- [48] Cho, C. S.; Kim, J. S.; Kim, H. S.; Kim, T.-J.; Shim, S. C. *Synthetic Commun.* **2001**, *31*, 3791-3797.
- [49] Hollmann, D.; Bähn, S.; Tillack, A.; Beller, M. *Angew. Chem. Int. Ed.* **2007**, *46*, 8291-8294.
- [50] Hollmann, D.; Bähn, S.; Tillack, A.; Beller, M. *Chem. Commun.* **2008**, 3199-3201.

- [51] Bähn, S.; Hollmann, D.; Tillack, A.; Beller, M. *Adv. Synth. Catal.* **2008**, 350, 2099-2103.
- [52] Hollmann, D.; Bähn, S.; Tillack, A.; Parton, R.; Altink, R.; Beller, M. *Tetrahedron Lett.* **2008**, 49, 5742-5745.
- [53] Blacker, A. J.; Stirling, M. J.; Page, M. I. *Org. Process Res. Dev.* **2007**, 11, 642-648.
- [54] Blacker, A. J.; Brown, S.; Clique, B.; Gourlay, B.; Headley, C. E.; Ingham, S.; Ritson, D.; Screen, T.; Stirling, M. J.; Taylor, D.; Thompson, G. *Org. Process Res. Dev.* **2009**, 13, 1370-1378.
- [55] Saidi, O.; Blacker, A. J.; Farah, M. M.; Marsden, S. P.; Williams, J. M. J. *Angew. Chem. Int. Ed.* **2009**, 48, 7375-7378.
- [56] Lorentz-Petersen, L. L. R.; Jensen, P.; Madsen, R. *Synthesis*, **2009**, 24, 4110-4112.
- [57] Cho, C. S. *Catalysis Communications*, **2006**, 7, 1012-1014.
- [58] Imm, S.; Bähn, S.; Tillack, A.; Mevius, K.; Neubert, L.; Beller, M. *Chem. Eur. J.* **2010**, 16, 2705-2709.
- [59] Grigg, R.; Mitchell, T. R. B.; Sutthivaiyakit, S. *Tetrahedron Lett.* **1981**, 22, 4107-4110.
- [60] Löfberg, C.; Grigg, R.; Whittaker, M. A.; Keep, A.; Derrick, A. *J. Org. Chem.* **2006**, 71, 8023-8027.
- [61] Löfberg, C.; Grigg, R.; Keep, A.; Derrick, A.; Sridharan, V.; Kilner, C. *Chem. Commun.* **2006**, 5000-5002.
- [62] Whitney, S.; Grigg, R.; Derrick, A.; Keep, A. *Org. Lett.* **2007**, 9, 3299-3302.
- [63] Grigg, R.; Whitney, S.; Sridharan, V.; Keep, A.; Derrick, A. *Tetrahedron*, **2009**, 65, 7468-7473.
- [64] Grigg, R.; Whitney, S.; Sridharan, V.; Keep, A.; Derrick, A. *Tetrahedron*, **2009**, 65, 4375-4383.
- [65] Jensen, T.; Madsen, R. *J. Org. Chem.* **2009**, 74, 3990-3992.

- [66] Slatford, P. A.; Whittlesey, M. K.; Williams, J. M. J. *Tetrahedron Lett.* **2006**, 47, 6787-6789.
- [67] Ledger, A. E. W.; Slatford, P. A.; Lowe, J. P.; Mahon, M. F.; Whittlesey, M. K.; Williams, J. M. J. *Dalton Trans.* **2009**, 716-722.
- [68] Grigg, R.; Löfberg, C.; Whitney, S.; Sridharan, V.; Keep, A.; Derrick, A. *Tetrahedron*, **2009**, 65, 849-854.
- [69] Morita, M.; Obora, Y.; Ishii, Y. *Chem. Commun.* **2007**, 2850-2852.
- [70] Taguchi, K.; Nakagawa, H.; Hirabayashi, T.; Sakaguchi, S.; Ishii, Y. *J. Am. Chem. Soc.* **2004**, 126, 72-73.
- [71] Iuchi, Y.; Hyotanishi, M.; Miller, B. E.; Maeda, K.; Obora, Y.; Ishii, Y. *J. Org. Chem.* **2010**, 75, 1803-1806.
- [72] Matsu-ura, T.; Sakaguchi, S.; Obora, Y.; Ishii, Y. *J. Org. Chem.* **2006**, 71, 8306-8308.
- [73] Koda, K.; Matsu-ura, T.; Sakaguchi, S.; Obora, Y.; Ishii, Y. *Chem. Lett.* **2009**, 38, 838-839.
- [74] Iuchi, Y.; Obora, Y.; Ishii, Y. *J. Am. Chem. Soc.* **2010**, 132, 2536-2537.
- [75] Hall, M. I.; Pridmore, S. J.; Williams, J. M. J. *Adv. Synth. Catal.* **2008**, 350, 1975-1978.
- [76] Pridmore, S. J.; Williams, J. M. J. *Tetrahedron Lett.* **2008**, 49, 7413-7415.
- [77] Edwards, M. G.; Williams, J. M. J. *Angew. Chem. Int. Ed.* **2002**, 41, 4740-4743.
- [78] Black, P. J.; Edwards, M. G.; Williams, J. M. J. *Eur. J. Org. Chem.* **2006**, 4367-4378.
- [79] Black, P. J.; Cami-Kobeci, G.; Edwards, M. G.; Slatford, P. A.; Whittlesey, M. K.; Williams, J. M. J. *Org. Biomol. Chem.* **2006**, 4, 116-125.
- [80] Shermer, D. J.; Slatford, P. A.; Edney, D. D.; Williams, J. M. J. *Tetrahedron Asymmetr.* **2007**, 18, 2845-2848.
- [81] Edwards, M. G.; Jazzar, R. F. R.; Paine, B. M.; Shermer, D. J.; Whittlesey, M. K.; Williams, J. M. J.; Edney, D. D. *Chem. Commun.* **2004**, 90-91.

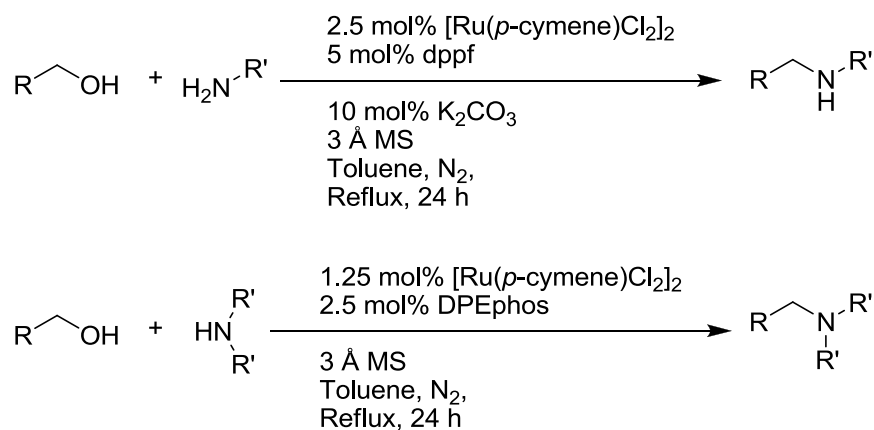
- [82] Fujita, K.; Asai, C.; Yamaguchi, T.; Hanasaka, F.; Yamaguchi, R. *Org. Lett.* **2005**, 7, 4017-4019.
- [83] Cheung, H. W.; Lee, T. Y.; Lui, H. Y.; Yeung, C. H.; Lau, C. P. *Adv. Synth. Catal.* **2008**, 350, 2975-2983.
- [84] Martínez, R.; Brand, G. J.; Ramón, D. J.; Yus, M. *Tetrahedron Lett.* **2005**, 46, 3683-3686.
- [85] Cho, C. S. *J. Mol. Catal. A-Chem.* **2005**, 240, 55-60.
- [86] Martínez, R.; Ramón, D. J.; Yus, M. *Tetrahedron*, **2006**, 62, 8988-9001.
- [87] Cho, C. S. *J. Mol. Catal. A-Chem.* **2007**, 267, 49-52.
- [88] Onodera, G.; Nishibayashi, Y.; Uemura, S. *Angew. Chem. Int. Ed.* **2006**, 45, 3819-3822.
- [89] Blank, B.; Kempe, R. *J. Am. Chem. Soc.* **2010**, 132, 924-925.
- [90] Flegeau, E. F.; Bruneau, C.; Dixneuf, P. H.; Jutand, A. *J. Am. Chem. Soc.* **2011**, 133, 10161-10170.
- [91] Jung, C.-K.; Garner, S. A.; Krische, M. J. *Org. Lett.* **2006**, 8, 519-522.
- [92] Komanduri, V.; Krische, M. J. *J. Am. Chem. Soc.* **2006**, 128, 16448-16449.
- [93] Barchuk, A.; Ngai, M.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2007**, 129, 8432-8433.
- [94] Bower, J.; Skucas, E.; Patman, R. L.; Krische, M. J. *J. Am. Chem. Soc.* **2007**, 129, 15134-15135.
- [95] Han, S. B.; Kim, I. S.; Han, H.; Krische, M. J. *J. Am. Chem. Soc.* **2009**, 131, 6916-6917.
- [96] Zbieg, J. R.; McInturff, E. L.; Krische, M. J. *Org. Lett.* **2010**, 12, 2514-2516.
- [97] Patman, R. L.; Chaulagain, M. R.; Williams, V. M.; Krische, M. J. *J. Am. Chem. Soc.* **2009**, 131, 2066-2067.
- [98] Williams, V. M.; Leung, J. C.; Patman, R. L.; Krische, M. J. *Tetrahedron*, **2009**, 65, 5024-5029.
- [99] Bower, J. F.; Patman, R. L.; Krische, M. J. *Org. Lett.* **2008**, 10, 1033-1035.

- [100] Han, H.; Krische, M. J. *Org. Lett.* **2010**, *12*, 2844-2846.
- [101] Zbieg, J. R.; Fukuzumi, T.; Krische, M. J. *Adv. Synth. Catal.* **2010**, *352*, 2416-2420.
- [102] Patman, R. L.; Williams, V. M.; Bower, J. F.; Krische, M. J. *Angew. Chem. Int. Ed.* **2008**, *47*, 5220-5223.
- [103] Zhang, Y. J.; Yang, J. H.; Kim, S. H.; Krische, M. J. *J. Am. Chem. Soc.* **2010**, *132*, 4562-4563.

2 RESULTS AND DISCUSSION I

2.1 Background

At the start of this work it was known that primary amines and secondary amines could be used in borrowing hydrogen methodology to synthesize secondary¹⁻⁴ and tertiary⁴⁻⁶ amines respectively. Indeed the Williams group had recently published both using the [Ru(*p*-cymene)Cl₂]₂/diphosphine combination (Scheme 1).⁷⁻⁸ However, the synthesis of primary amines using ammonia or an ammonia equivalent had not yet been realised and our initial work focused on approaches to solving this problem.



Scheme 1 - Known Amine Formation Using Borrowing Hydrogen

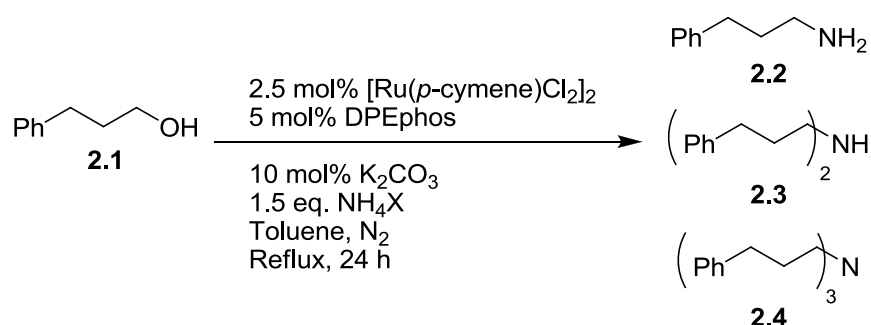
More recently, Milstein,⁹ Vogt¹⁰ and Beller¹¹⁻¹² have been successful in applying ammonia gas at elevated pressures to access primary amines selectively.

2.2 Initial Studies

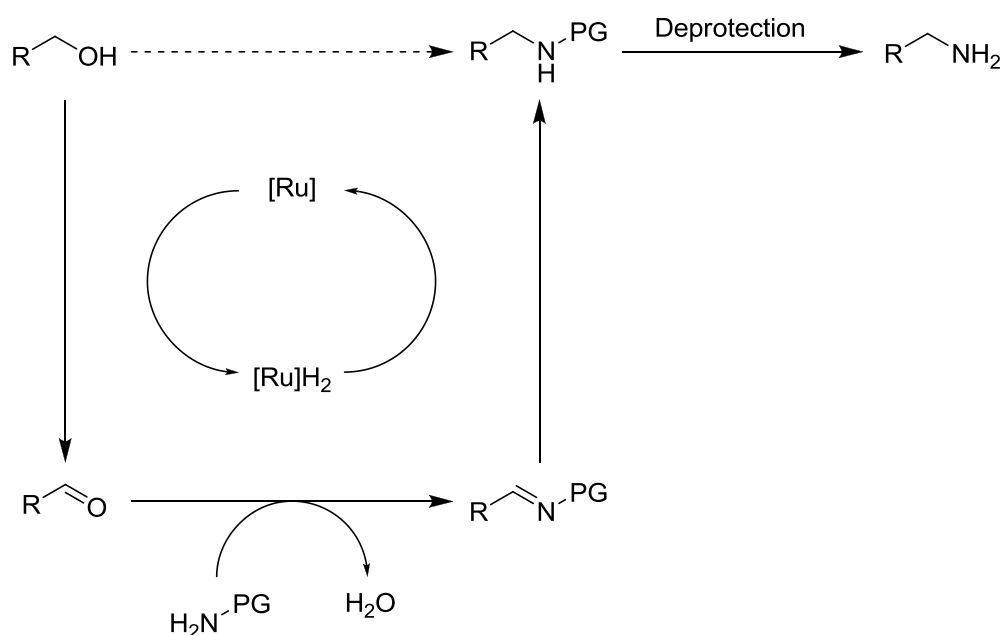
Initially we considered potential sources of ammonia that would be suitable to access primary amines (Scheme 2).

However, all the ammonium salts⁸ and solutions¹³⁻¹⁴ used, even in large excess, showed no indication of the primary amine (**2.2**) by analysis using mass spectrometry. Instead a mixture of secondary (**2.3**) and tertiary amine (**2.4**) was detected. The only exception to this was when the atmosphere of the reaction was changed from nitrogen to ammonia. In this case, the primary amine (**2.2**) was observed by mass spectrometry since analysis of the ¹H NMR was difficult due to the overlapping signals of the secondary (**2.3**) and tertiary amine (**2.4**). Further analysis

of the product distribution leads to two significant conclusions. The first and most important is that the reaction is indeed working and forming the desired primary amine (**2.2**), unfortunately this is then more nucleophilic than the source of ammonia, and so goes on to react further giving the observed mixtures of secondary and tertiary amines. The second is that the distribution of the mixture between secondary and tertiary amine can be determined by the acidity of the counter-ion, which has also been noted by Yamaguchi and Fujita.¹⁵ Since this initial work, urea has also been shown to be a useful source of ammonia, although it too leads to over-alkylation.¹⁶

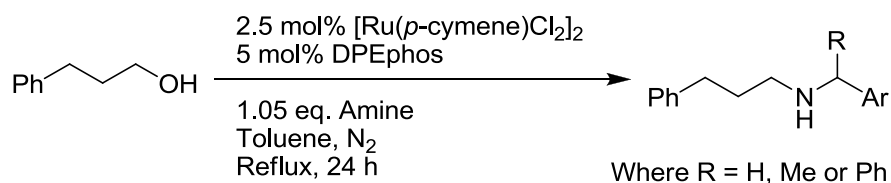


Scheme 2 - Ammonia Source Screening Reaction



Scheme 3 - Masked Amine Approach to Primary Amine Synthesis

Having established that only the use of high pressures of ammonia could lead to selective primary amine formation, an alternative approach was sought that could be applied by the large majority of synthetic chemists without the need for specialist high pressure apparatus. It was decided to use a masked amine, which would result in



Scheme 4 - Synthesis of Benzylic Secondary Amines

Entry ^a	Amine	Conversion (%) ^{b,c}	Yield (%) ^d	Product
1	 2.5	100	-	-
2	 2.6	0	-	-
3	 2.7	100	-	-
4	 2.8	100	-	-
5	 2.9	100	-	-
6	 2.10	100	85	2.13
7	 2.11	100	79	2.14
8	 2.12	60	54	2.15

^aConditions: 3-Phenyl-1-propanol (3 mmol), amine (3.15 mmol), [Ru(*p*-cymene)Cl₂]₂ (2.5 mol%), DPEphos (5 mol%), toluene (3 mL), reflux, 24 h; ^bConversion determined by consumption of alcohol; ^cDetermined by ¹H NMR; ^dIsolated yield of secondary amine.

Table 1 - Benzylic Protecting Groups

the product being a protected primary amine. Once this had been made, a second deprotection step could then be carried out *in situ* to yield the primary amine in a two-

step one-pot process (Scheme 3). This would avoid the undesirable formation of the secondary and tertiary amine previously observed.

Literature precedent¹⁷⁻¹⁸ indicated that benzylic amines would provide a readily available source of masked amine; being both cheap and widely available. As such a screen of known benzylic amine protecting groups (Scheme 4 & Table 1) was run with the secondary amines being isolated in each case to prove the intermediate structures formed.

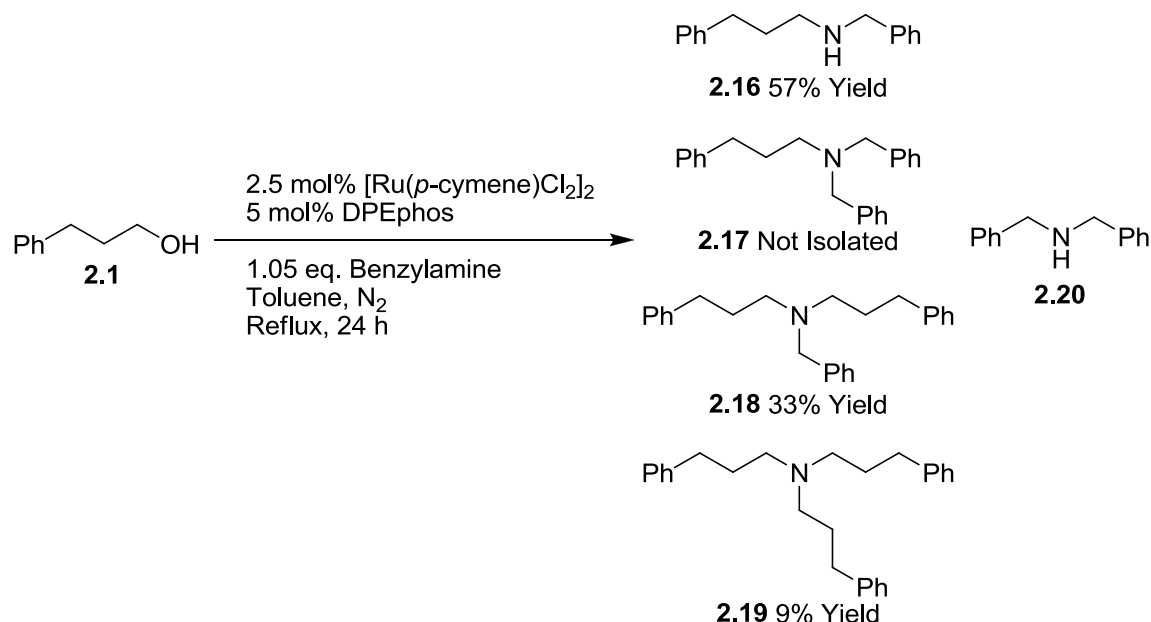
Interestingly, 100% conversion of the alcohol was observed with benzylamine (**2.5**), but analysis of the reaction mixture by mass spectrometry and ¹H NMR showed a mixture of amine products. Isolation by silica column chromatography proved that these compounds were not present as traces, but as significant products. Isolation and characterisation of each one was conducted in order to prove the structures (Scheme 5). Further analysis by mass spectrometry and ¹H NMR also revealed similar mixtures for the other benzylic amines tested (Entries 3-5, Table 1).

Dibenzylamine (**2.6**) did not react at all (Entry 2, Table 1) which was surprising considering that it has been reported to react by the Williams group under identical conditions with benzyl alcohol. As mentioned above, other benzylic amines also gave similar results (Entries 3-5, Table 1) to benzylamine. However, when the α -position was hindered, either with a methyl (**2.10**) or a phenyl (**2.11**) the reaction proceeded cleanly to the desired secondary amine with good yields (Entries 6 & 7, Table 1). Even when the sterically crowded tritylamine (**2.12**) was used, the reaction still proceeded, although with a lower conversion and isolated yield (Entry 8, Table 1).

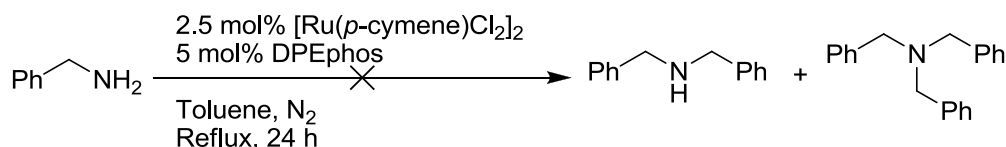
Analysis, isolation and characterisation of the products from the benzylamine reaction suggested that amine condensation could be a pathway in operation. This was tested by attempting the self-condensation of benzylamine under the same reaction conditions (Scheme 6). Under these conditions the reaction did not occur, suggesting that either the alcohol or the water generated is an important factor in the condensation. Indeed the cross coupling of triethylamine and 4-methoxyaniline (**2.21**) does occur at higher temperatures when catalytic water is present (Scheme 7). Thus, the amine condensation cannot be ruled out as a possible reaction pathway.

The desired product (**2.16**, Scheme 5) is the major product, formed in 57% isolated yield, and it is clear to see how the diphenylpropyl tertiary amine (**2.18**) can be formed from this initial product by reaction with another molecule of alcohol. Dibenzylamine (**2.20**) can be assumed to be occurring *via* amine oxidation; the self-

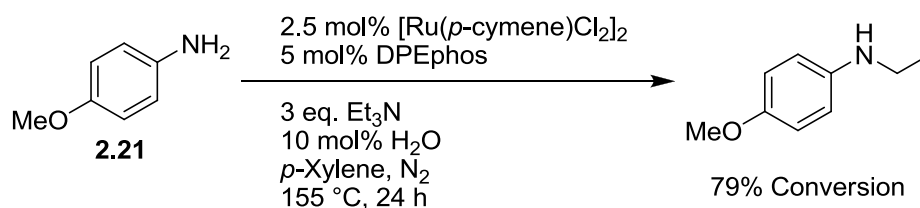
condensation of benzylamine by transition metal catalysts is well reported in the literature.¹⁹⁻²³ Only traces of the dibenzyl tertiary amine (**2.17**) were formed as it is only detected by analysis using mass spectrometry and is not observed by TLC.



Scheme 5 - Products Isolated From the Use of Benzylamine



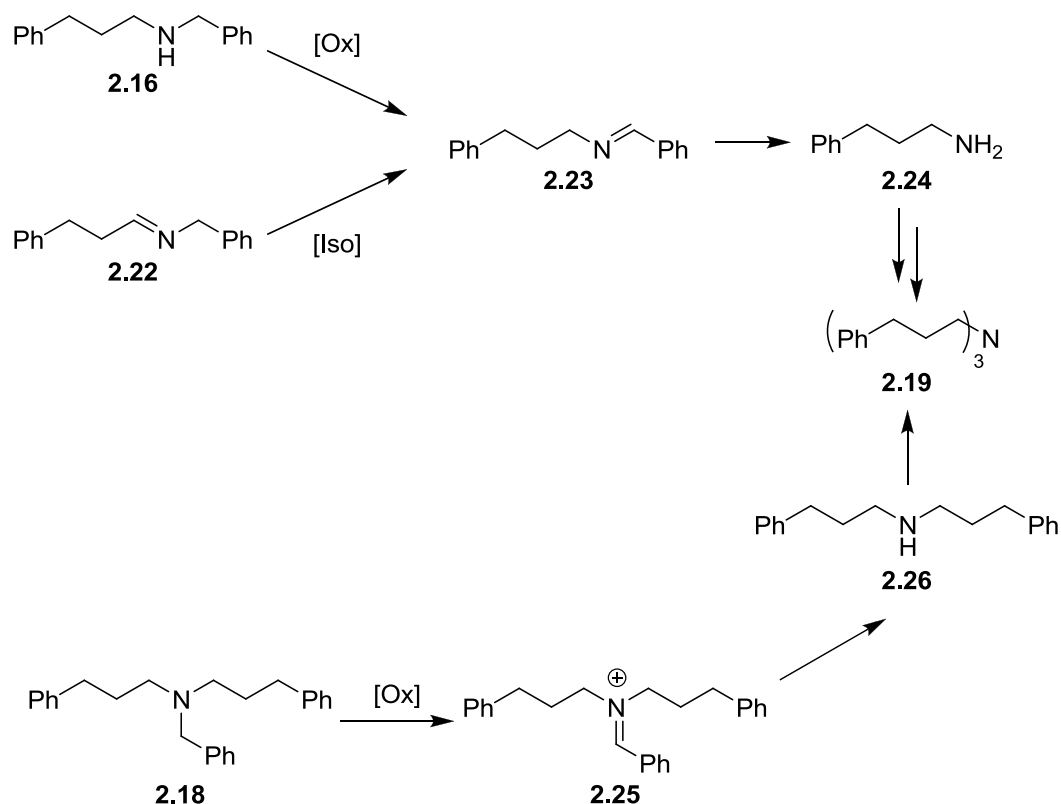
Scheme 6 - Self Condensation of Benzylamine



Scheme 7 - Cross-coupling of Amines

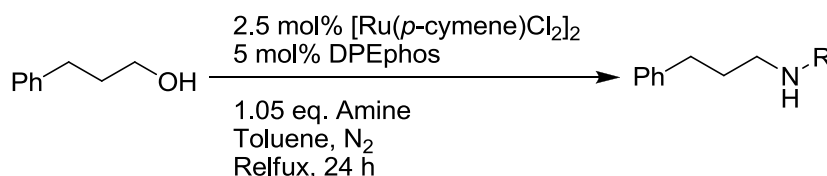
This indicates that it is a minor product and fits with the previously observed poor reaction of dibenzylamine with 3-phenyl-1-propanol (Entry 2, Table 1). The most interesting result is the symmetric tertiary amine (**2.19**) as this could form by three possible routes; oxidation of **2.16**, oxidation of **2.18** or isomerisation of the imine intermediate (Scheme 8). The oxidation of **2.18** seems to be the least likely, as none of the intermediate **2.26** was detected by either ^1H NMR or mass spectrometry. The selective oxidation of **2.16** to **2.23** followed by hydrolysis to the primary amine (**2.24**)

which then reacts with two more molecules of alcohol is possible. However, the hydrolysis would require water to be present which would be present only in small quantities due to the reaction being run in toluene at reflux. This would account for the small amount of this material that was isolated (9%). The final possibility is the isomerisation of intermediate imine **2.22** to an alternative imine **2.23** again followed by hydrolysis to the primary amine. Isomerisation of imines has been reported previously²⁴ and in this case would be thermodynamically favourable, setting up an extended delocalised system with the aromatic ring. Either of these final two mechanisms could be the one in operation, or a combination of both, however, further study to determine this was not followed up as this was not the aim of the project.



Scheme 8 - Possible Routes to 2.19

Both *tert*-butylamine (**2.27**) and *tert*-octylamine (**2.28**) gave complete conversion with high isolated yields (Entries 1 & 2, Table 2). Both allyl and diallyl amine gave mixtures of products including molecules that had the allyl double bond reduced and so these two examples were not carried forward. 4-Methoxyaniline (**2.31**) gave a good conversion but lower isolated yield. Analysis of the ¹H NMR of the crude reaction (Entry 5, Table 2) showed three peaks corresponding to the methoxy group, suggesting some remaining starting material, product and a by-product.



Scheme 8 - Synthesis of Other Secondary Amines

Entry ^a	Amine	Conversion (%) ^{b,c}	Yield (%) ^d	Product
1	 2.27	100	61	2.32
2	 2.28	100	89	2.33
3	 2.29	N.D.	-	-
4	 2.30	N.D.	-	-
5	 2.31	100	60	2.34

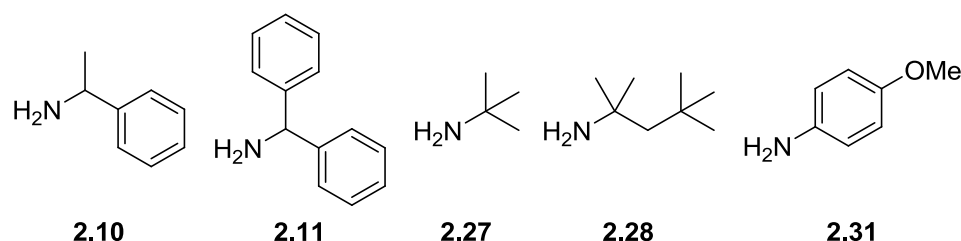
^aConditions: 3-Phenyl-1-propanol (3 mmol), amine (3.15 mmol), $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$ (2.5 mol%), DPEphos (5 mol%), toluene (3 mL), reflux, 24 h; ^bConversion determined by consumption of alcohol; ^cDetermined by ^1H NMR; ^dIsolated yield.

Table 2 - Other Protecting Groups

On the basis of the results discussed above the following amines were picked out for consideration; 1-phenethylamine (**2.10**), benzhydrylamine (**2.11**), *tert*-butylamine (**2.27**), *tert*-octylamine (**2.28**) and 4-methoxyaniline (**2.31**) (Scheme 9). It is worth noting that sulfonamides which might have been good substrates were not considered as this work was being done by another member of the group.

In order to determine which to take forward for further use, the cost and method of deprotection for each amine was considered. *tert*-Butylamine (**2.27**) and *tert*-octylamine (**2.28**) were discarded due to the strongly acidic conditions required for deprotection.²⁵⁻³³ 4-Methoxyaniline (**2.31**) was discarded due to the safety concerns of combining an oxidising agent, even a mild one, with a transition metal.³⁴⁻³⁸ This left two amines, 1-phenethylamine (**2.10**) and benzhydrylamine (**2.11**).

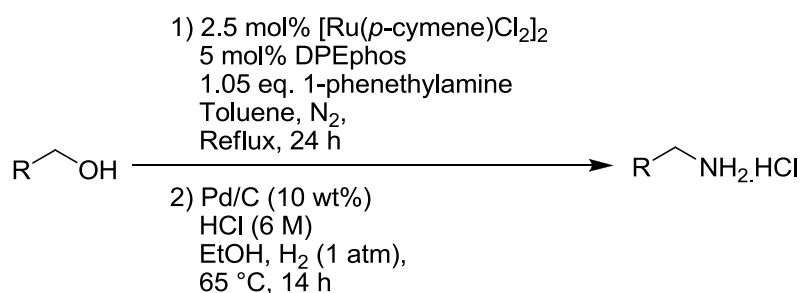
Both protecting groups can be removed by hydrogenation,³⁹⁻⁴⁰ however, benzhydrylamine offers two other options using acidic⁴¹ or oxidative⁴² conditions. A cost comparison of the two amines shows that benzhydrylamine, at 23 pence per mmol, is significantly more expensive than 1-phenethylamine which only costs 1 pence per mmol. Added to this is the atom economy argument for using 1-phenethylamine due to its lower molecular weight and number of atoms; so 1-phenethylamine was chosen as the amine for further studies. A screen of the literature for hydrogenation conditions⁴³⁻⁴⁷ to remove the 1-phenethyl group *in situ* led to conditions that work for the reaction mixture and result in successful deprotection.⁴⁸⁻⁴⁹



Scheme 9 - Final Amines For Consideration

2.3 Reaction Scope

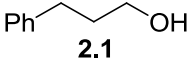
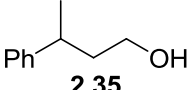
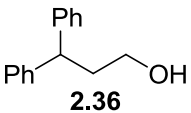
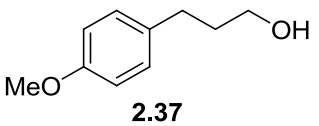
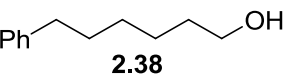
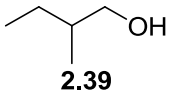
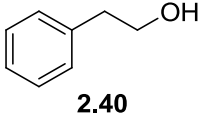
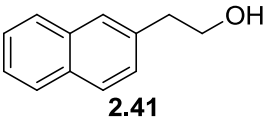
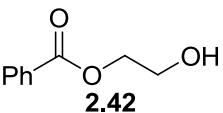
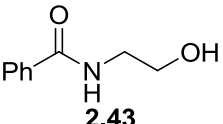
Having established a set of conditions (Scheme 10), a series of alcohols was screened to determine the tolerance of the reaction to alternative substrates (Table 3).



Scheme 10 - Optimised Conditions

The first set of results was good (Entries 1-6, Table 3) with yields from 52-85%. However, when the substrate range was expanded to phenethyl scaffolds (Entries 7 & 8, Table 3) problems were encountered (the phenethyl structure is important in neurotransmitters). While secondary amine was formed in good conversion (Entries 7 & 8, Table 3), the deprotection to the primary amine proved problematic. The deprotection of the phenethyl compound (Entry 7, Table 3) gave a mixture of 1-

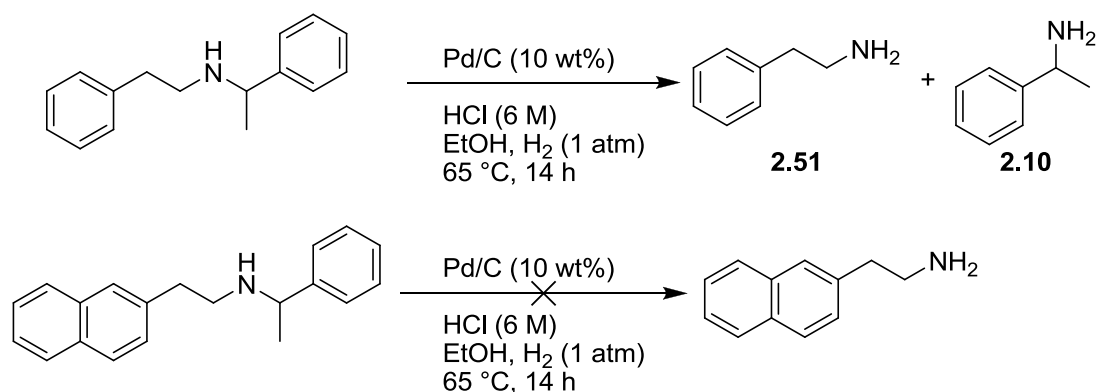
phenethylamine (**2.10**) and 2-phenethylamine (**2.40**) (Scheme 11), indicating that the deprotection was not selective. In the case of the naphthyl (Entry 8, Table 3), deprotection was unsuccessful, the secondary amine was recovered unchanged (Scheme 11).

Entry ^a	Alcohol	Yield (%) ^{b,c}	Product
1	 2.1	85	2.44
2	 2.35	52	2.45
3	 2.36	75	2.46
4	 2.37	54	2.47
5	 2.38	65	2.48
6	 2.39	67	2.49
7	 2.40	100 ^d	-
8	 2.41	79 ^e	2.50
9	 2.42	0 ^d	-
10	 2.43	100 ^d	-

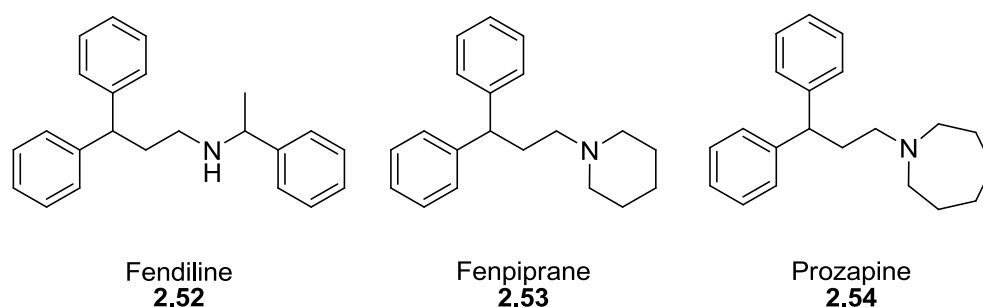
^aConditions: Alcohol (3 mmol), amine (3.15 mmol), [Ru(*p*-cymene)Cl₂]₂ (2.5 mol%, DPEphos (5 mol%), Toluene (3 mL), reflux, 24 h, then Pd/C (10 wt%, 10 mol%), EtOH (11 mL), HCl (6 M, 1.1 mL), 65 °C, 14 h; ^bIsolated Yield; ^cIsolated as the HCl salt; ^dConversion to the secondary amine product; ^eIsolated as the secondary amine.

Table 3 - Results of Two-Step Primary Amine Synthesis

Problems were also encountered when other functionality was introduced (Entries 9 & 10, Table 3). No coupling was observed with the amine when an ester group was present, suggesting the alcohol and ester (Entry 9, Table 3) were chelating to the catalyst. Formation of the secondary amine was more successful in the presence of an amide group (Entry 10, Table 3), however, again deprotection was unsuccessful returning starting material under the conditions applied. The results of this work together with work on the sulfonamides was published.⁵⁰



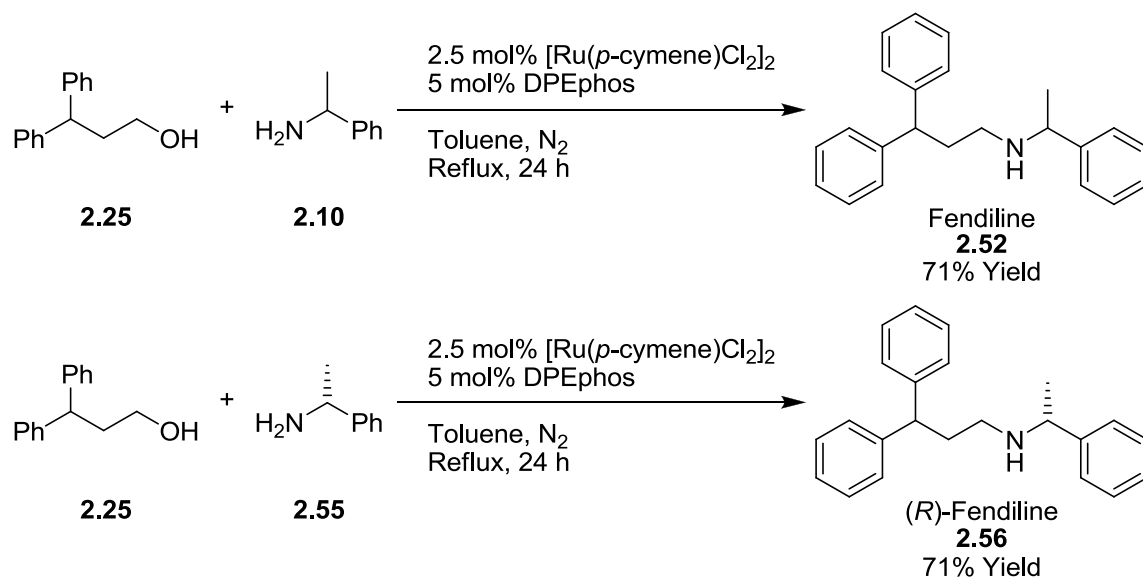
Scheme 11 - Deprotection Problems with Phenethyl Scaffolds



Scheme 12 - Pheniramines that are APIs

During the course of this work, it was noticed that one of the intermediates was actually an Active Pharmaceutical Ingredient (API). Indeed, the intermediate secondary amine produced from the reaction of 3,3-diphenyl-1-propanol (**2.36**) with 1-phenethylamine (**2.10**) is Fendiline (**2.52**) which has anti-hypertensive and anti-anginal properties.⁵¹⁻⁵² The 3,3-diphenyl-1-propanamine moiety is present in quite a few APIs (Scheme 12) with Fenpiprane (**2.53**) being spasmolytic and antiallergic and Prozapine (**2.54**) being spasmolytic and choleric.⁵³⁻⁵⁴ As such, Fendiline (**2.52**) was isolated in 71% yield. It was also possible to make a single enantiomer of Fendiline (**2.52**) by starting with an enantiopure amine, in this case the (*R*)-enantiomer (**2.55**), which produced the enantiomerically pure product (**2.45**) in identical yield to the

racemic reaction, and without any racemisation being detected by ^1H NMR (Scheme 13) in the presence of (*S*)-(-)-*O*-Acetylmandelic acid.⁵⁵



Scheme 13 – Fendiline (2.52) & (*R*)-Fendiline (2.56) Results

2.4 CHAPTER SUMMARY

- A two-step one-pot synthesis of alkyl primary amines from primary alcohols was achieved.
- The reaction will tolerate a range of substrates, but not phenethyl scaffolds.
- Other functionality present in a 1,2-substitution pattern can lead to problems with either step.
- An intermediate secondary amine which was also an API could be isolated as a single enantiomer in good yield.

2.5 References

- [1] Grigg, R.; Mitchell, T. R. B.; Sutthivaiyakit, S.; Tongpenyai, N. *J. Chem. Soc. Chem. Commun.* **1981**, 611-612.
- [2] Fujita, K.; Li, Z.; Ozeki, N.; Yamaguchi, R. *Tetrahedron Lett.* **2003**, *44*, 2687-2690.
- [3] Hollmann, D.; Tillack, A.; Michalik, D.; Jackstell, R.; Beller, M. *Chem. Asian J.* **2007**, *2*, 403-410.
- [4] Cami-Kobeci, G.; Slatford, P. A.; Whittlesey, M. K.; Williams, J. M. J. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 535-537.
- [5] Watanabe, Y.; Tsuji, Y.; Ohsugi, Y. *Tetrahedron Lett.* **1981**, *22*, 2667-2670.
- [6] Tillack, A.; Hollmann, D.; Mevius, K.; Michalik, D.; Bähn, S.; Beller, M. *Eur. J. Org. Chem.* **2008**, 4745-4750.
- [7] Hamid, M. H. S. A.; Williams, J. M. J. *Chem. Commun.* **2007**, 725-727.
- [8] Hamid, M. H. S. A.; Williams, J. M. J. *Tetrahedron Lett.* **2007**, *48*, 8263-8265.
- [9] Gunanathan, C.; Milstein, D. *Angew. Chem. Int. Ed.* **2008**, *47*, 8661-8664.
- [10] Pinggen, D.; Müller, C.; Vogt, D. *Angew. Chem. Int. Ed.* **2010**, *49*, 8130-8133.
- [11] Imm, S.; Bähn, S.; Neubert, L.; Neumman, H.; Beller, M. *Angew. Chem. Int. Ed.* **2010**, *49*, 8126-8129.
- [12] Imm, S.; Bähn, S.; Zhang, M.; Neubert, L.; Neumman, H.; Klasovsky, F.; Pfeffer, J.; Haas, T.; Beller, M. *Angew. Chem. Int. Ed.* **2011**, *50*, 7599-7603.
- [13] Kawahara, R.; Fujita, K.; Yamaguchi, R. *J. Am. Chem. Soc.* **2010**, *132*, 15108-15111.
- [14] Kawahara, R.; Fujita, K.; Yamaguchi, R. *Adv. Synth. Catal.* **2011**, *353*, 1161-1168.
- [15] Yamaguchi, R.; Kawagoe, Asai, C.; Fujita, K. *Org. Lett.* **2008**, *10*, 181-184.

- [16] Yamaguchi, K.; He, J.; Oishi, T.; Mizuno, N. *Chem. Eur. J.* **2010**, *16*, 7199-7207.
- [17] Wuts, P. G. M.; Greene, T. W. *Protective Groups in Organic Synthesis*; John Wiley & Sons: New York, NY, 1981.
- [18] Kociński, P. J. *Protecting Groups*; Stuttgart, GTV, 2000.
- [19] Bui-The-Khai; Concilio, C.; Porzi, G. *J. Org. Chem.* **1981**, *46*, 1759-1760.
- [20] Bui-The-Kai; Concilio, C.; Porzi, G. *J. Organomet. Chem.* **1981**, *208*, 249-251.
- [21] Murahashi, S.-I.; Yoshimura, N.; Tsumiyama, T.; Kojima, T. *J. Am. Chem. Soc.* **1983**, *105*, 5002-5011.
- [22] Saidi, O.; Blacker, A. J.; Farah, M. M.; Marsden, S. P.; Williams, J. M. J. *Angew. Chem. Int. Ed.* **2009**, *48*, 7375-7378.
- [23] Lorentz-Petersen, L. L. R.; Jensen, P.; Madsen, R. *Synthesis* **2009**, *24*, 4110-4112.
- [24] Yamagishi, T.; Mizushima, E.; Sato, H.; Yamaguchi, M. *Chem. Lett.* **1998**, *27*, 1255-1256.
- [25] Englert, H. C.; Gerlach, U.; Goegelien, H.; Hartung, J.; Heitsch, H.; Mania, D.; Scheidler, S. *J. Med. Chem.* **2001**, *44*, 1085-1098.
- [26] Li, J.; Smith, D.; Wong, H. S.; Campbell, J. A.; Meanwell, N. A.; Scola, P. M. *Synlett*, **2006**, *5*, 725-728.
- [27] Dhimitruka, I.; Bobko, A. A.; Hadad, C. M.; Zweier, J. L.; Khramtsov, V. V. *J. Am. Chem. Soc.* **2008**, *130*, 10780-10787.
- [28] Meredith, E. L.; Beattie, K.; Burgis, R.; Capparelli, M.; Chapo, J.; DiPietro, L.; Gamber, G.; Enyedy, I.; Hood, D. B.; Hosagrahara, V.; Jewell, C.; Koch, K. A.; Lee, W.; Lemon, D. D.; McKinsey, T. A.; Miranda, K.; Pagratis, N.; Phan, D.; Plato, C.; Rao, C.; Rozhitskaya, O.; Soldermann, N.; Springer, C.; van Eis, M.; Vega, R. B.; Yan, W.; Zhu, Q.; Monovich, L. G. *J. Med. Chem.* **2010**, *53*, 5422-5438.
- [29] Veljkovic, I.; Zimmer, R.; Reissig, H.-U.; Brüggam, I.; Hartl, H. *Synthesis*, **2006**, *16*, 2677-2684.

- [30] DiMauro, E. F.; Kennedy, J. M. *J. Org. Chem.* **2006**, *72*, 1013-1016.
- [31] Krasavin, M.; Shkavrov, S.; Parchinsky, V.; Bukhryakov, K. *J. Org. Chem.* **2009**, *74*, 2627-2629.
- [32] Kysil, V.; Khvat, A.; Tsirolnikov, S.; Tkachenko, S.; Williams, C.; Churakova, M.; Ivachtchenko, A. *Eur. J. Org. Chem.* **2010**, 1525-1543.
- [33] Bouma, M.; Masson, G.; Zhu, J. *J. Org. Chem.* **2010**, *75*, 2748-2751.
- [34] Zhao, L.; Li, C.-J. *Angew. Chem. Int. Ed.* **2008**, *47*, 7075-7078.
- [35] Balthaser, B. R.; McDonald, F. E. *Org. Lett.* **2009**, *11*, 4850-4853.
- [36] De Lamo Marin, S.; Martens, T.; Mioskowski, C.; Royer, J. *J. Org. Chem.* **2005**, *70*, 10592-10595.
- [37] De Lamo Marin, S.; Catala, C.; Ratna Kumar, S.; Valleix, A.; Wagner, A.; Mioskowski, C. *Eur. J. Org. Chem.* **2010**, 3985-39879.
- [38] Verkade, J. M. M.; van Hemert, L. J. C.; Quaedflieg, P. J. L. M.; Alsters, P. L.; van Delft, F. L.; Rutjes, F. P. J. T. *Tetrahedron Lett.* **2006**, *47*, 8109-8113.
- [39] McLean, T. H.; Parrish, J. C.; Braden, M. R.; Marona-Lewicka, D.; Gallardo-Godoy, A.; Nichols, D. E. *J. Med. Chem.* **2006**, *49*, 5794-5803.
- [40] Ooi, T.; Sakai, D.; Takeuchi, M.; Tayama, E.; Maruoka, K. *Angew. Chem. Int. Ed.* **2003**, *42*, 5868-5870.
- [41] Dangerfield, E. M.; Timmer, M. S. M.; Stocker, B. L. *Org. Lett.* **2009**, *11*, 535-538.
- [42] Sampson, P. B.; Honek, J. F. *Org. Lett.* **1999**, *1*, 1395-1397.
- [43] Avila-Ortiz, C. G.; Reyes-Rangel, G.; Juaristi, E. *Tetrahedron* **2005**, *61*, 8372-8381.
- [44] Díaz, M.; Branchadell, V.; Oliva, A.; Ortuño, R. M. *Tetrahedron* **1995**, *51*, 11841-11854.
- [45] Shustov, G. V.; Rauk, A. *Tetrahedron: Asymmetry*, **1996**, *7*, 699-708.
- [46] Singh, R. K.; Sinha, N.; Jain, S.; Salman, M.; Naqvi, F.; Anand, N. *Tetrahedron*, **2005**, *61*, 8868-8874.

- [47] Lloyd, J.; Schmidt, J. B.; Rovnyak, G.; Ahmad, S.; Atwal, K. S.; Bisaha, S. N.; Doweiko, L. M.; Stein, P. D.; Traeger, S. C.; Mathur, A.; Lee Conder, M.; DiMarco, J.; Harper, T. W.; Jenkins-West, T.; Levesque, P. C.; Normandin, D. E.; Russell, A. D.; Serafino, R. P.; Smith, M. A.; Lodge, N. J. *J. Med. Chem.* **2001**, *44*, 3764-3767.
- [48] Davies, S. G.; Ichihara, O. *Tetrahedron: Asymmetry*, **1991**, *2*, 183-186.
- [49] Fujita, K.; Fujii, T.; Yamaguchi, R. *Org. Lett.* **2004**, *6*, 3525-3528.
- [50] Lamb, G. W.; Watson, A. J. A.; Jolley, K. E.; Maxwell, A. C.; Williams, J. M. J. *Tetrahedron Lett.* **2009**, *50*, 3374-3377.
- [51] Wilkinson, J. A.; Rossington, S. B.; Coe, N. A.; Hirst, N.; McGown, A. T.; Leonard, J.; Hussain, N. *Lett. Drug Des. Discov.* **2007**, *4*, 246-248.
- [52] Wilkinson, J. A.; Foretia, D.; Rossington, S.; Heagerty, A.; Leonard, J.; Hussain, N.; Austin, C.; *Eur. J. Pharmacol.* **2007**, *561*, 160-163.
- [53] Rische, T.; Eilbracht, P. *Tetrahedron* **1999**, *55*, 1915-1920.
- [54] Ahmed, M.; Buch, C.; Routaboul, L.; Jackstell, R.; Klein, H.; Spannenberg, A.; Beller, M. *Chem. Eur. J.* **2007**, *13*, 1594-1601.
- [55] Sugiyama, S.; Morishita, K.; Chiba, M.; Ishii, K. *Heterocycles* **2002**, *57*, 637-648.

3 RESULTS AND DISCUSSION II

3.1 Background

The use of ammonia and its salts in borrowing hydrogen reactions have been shown to form symmetric tertiary amines when reacted with an excess of alcohol.¹⁻⁵ Previous work (Chapter 2) demonstrated that even when using a large excess of ammonia there was little control in the selectivity of product formation between primary, secondary and tertiary amines. The formation of symmetric tertiary amines using borrowing hydrogen methodology while interesting, has limited synthetic utility. However, non-symmetric tertiary amines, where one or more groups are different, are present in many pharmaceuticals (Figure 1) and are often key to the API's characteristics. The tertiary amine moiety can aid binding in the active site, restrict degrees of rotation in the molecule, or modify the log *P* to improve solubility and/or permeability *in vivo*.

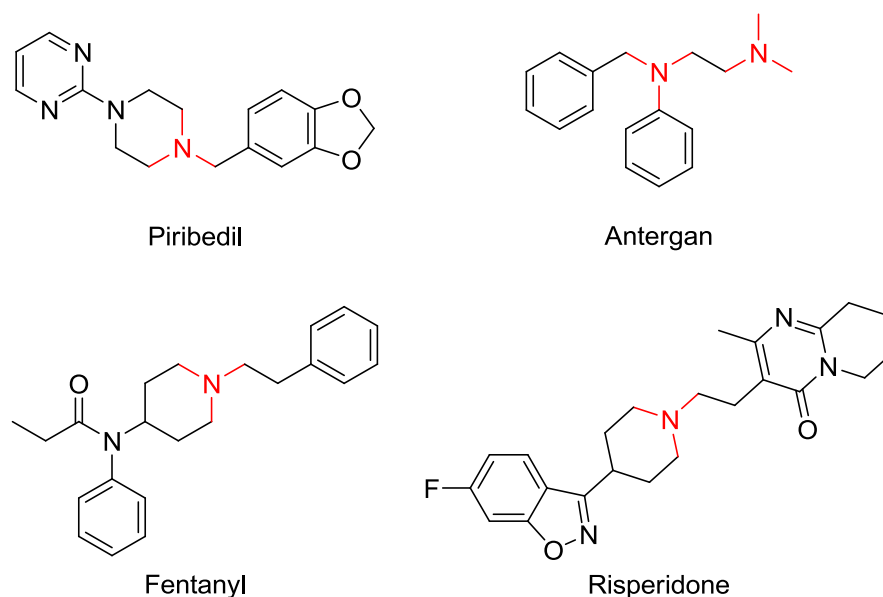
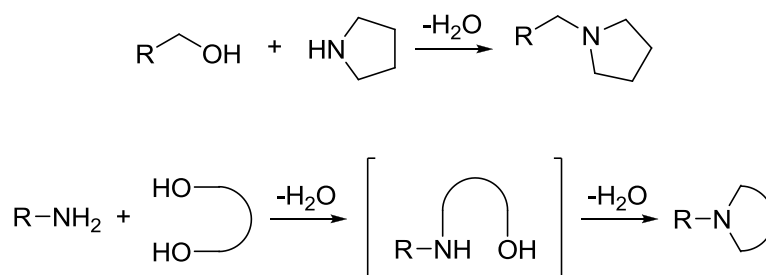
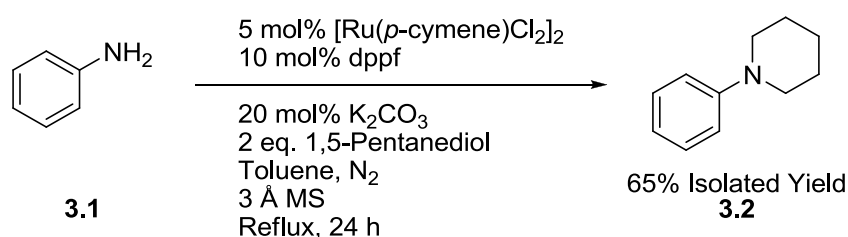


Figure 1 - Marketed Drugs Containing Non-symmetric Tertiary Amines

Synthesis of non-symmetric tertiary amines using borrowing hydrogen methodologies has focused on the alkylation of secondary amines preventing the problems of over-alkylation and by-product formation.⁶⁻¹⁵ An alternative approach to this motif would take advantage of the reactivity of the nitrogen atom in primary amines and seek to alkylate twice with two alcohols tethered together, a diol, thus forming a cyclic tertiary amine (Scheme 1).

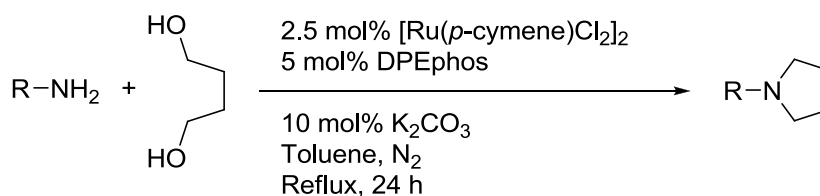
**Scheme 1 - Possible Routes to Asymmetric Tertiary Amines**

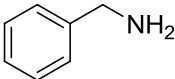
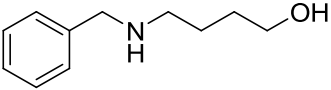
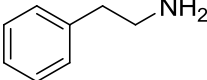
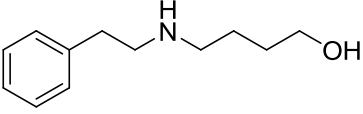
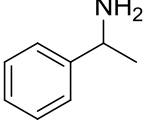
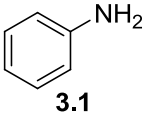
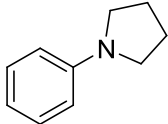


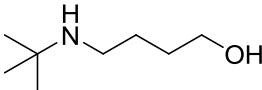
Examples of this approach were already present in the literature^{12,15-18} with good yields and substrate scope, however, there was only one example using the ruthenium catalyst system developed by the Williams group¹⁹ which gave comparatively low yields despite using high catalyst loadings (Scheme 2).

**Scheme 2 - Previous Example from the Williams Group¹⁹**

3.2 Initial Studies

Initial work focused on screening a range of primary amines and 1,4-butanediol with the [Ru(*p*-cymene)Cl₂]₂/DPEphos system shown to be active for the synthesis of tertiary amines by the Williams group,¹⁰ using K₂CO₃ as an activating base¹⁹ (Scheme 3).

**Scheme 3 - Initial Reaction Conditions**

Entry ^a	Amine	Product
1 ^b		
2 ^b		
3		Unclear
4 ^c	 3.1	
5		Unclear
6 ^b		

^aConditions: [Ru(*p*-cymene)Cl₂] (2.5 mol%), DPEphos (5 mol%), K₂CO₃ (10 mol%), amine (1 mmol), diol (1.5 mmol), toluene (1 mL), reflux, 24 h;

^bDetermined by mass spec; ^cDetermined by ¹H NMR.

Table 1 - Initial Amine Screen

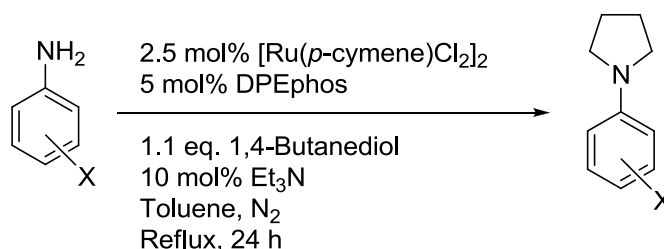
Analysis of the crude reaction mixtures by ¹H NMR for all amines showed a large number of different compounds present except in the case of aniline (Entry 4, Table 1) (**3.1**) where the product was clearly visible by the symmetry of the signals observed. This was further confirmed by analysis of mass spectra and comparison of the ¹H NMR with literature references. Further analysis of the other samples by mass spectrometry revealed that the major product formed was the amino-alcohol in most cases (Entries 1, 2 & 6, Table 1).

While the initial results were disappointing, the formation of the desired product with aniline was encouraging and demonstrated that the reaction did proceed at a lower catalyst loading than previously reported.¹⁹

Previous work in the literature applying borrowing hydrogen methodologies has shown that the choice of activating base has an important effect on the reaction. Furthermore, the formation of the mono-alkylated product in 50% of the reactions illustrated a similarity to the formation of secondary amines previously reported with a similar catalyst.¹⁹ Comparison of the formation of secondary and tertiary amine formation reported by the Williams group showed that no base was required for

tertiary amine formation.¹⁰ As such a screen of activating bases was conducted, revealing that all gave similar mixtures of products except for triethylamine. Analysis of the crude reaction mixture, by ¹H NMR, in this case showed the presence of the desired product and some γ -butyrolactone formed by dehydrogenative lactonisation²⁰⁻²³ of the excess diol. It was then possible to reduce the excess of diol from 1.5 to 1.1 equivalents while still retaining high conversion. However, it was not possible to reduce the catalyst loading below 5 mol% of ruthenium without hampering conversion.

3.3 Reaction Scope



Scheme 4 - Optimised Reaction Conditions

Having established a set of conditions (Scheme 4), a series of anilines was screened to determine the tolerance of the reaction to alternative substrates (Table 2).

The results were generally good with isolated yields >60%. The inclusion of a methyl substituent was well tolerated in the ortho (**3.6**), meta (**3.9**), and para (**3.13**) positions. Meta substituents were also well tolerated, although a lower yield was recorded for the trifluoromethyl compound (**3.11**) but even with a nitro group (**3.12**) present on the ring the desired product could still be obtained in 50% yield. Substitution at the 2- and 4-positions gave varying results dependent on the electronic effect of the substitution. Substrates with strong electron withdrawing groups such as cyano (**3.19**) or nitro (**3.20**) gave no conversion, even on increased heating (155 °C). However, weaker electron withdrawing groups such as fluoro (**3.4** & **3.14**) and chloro (**3.5**, **3.10** & **3.15**) gave yields determined by the proximity to the nitrogen, with para-substitution giving higher yields than ortho. In the case of esters (**3.18**) the yield could be improved by increased heating (155 °C) using *p*-xylene as solvent. Analysis of the entire set illustrates that the yield is determined by the nucleophilicity of the nitrogen, which is determined by the position and electronic nature of the substituent on the aromatic ring with no exceptions.

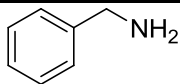
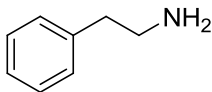
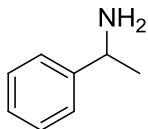
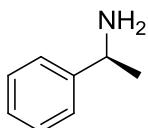
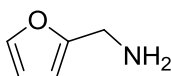
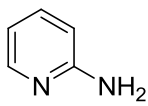
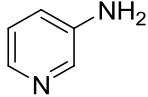
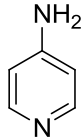
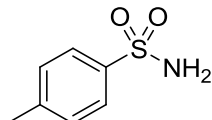
Entry ^a	Substitution	Isolated Yield (%)	Product
1	None	78	3.3
2	2-F	33	3.4
3	2-Cl	24 ^b	3.5
4	2-Me	76	3.6
5	2-NO ₂	0 ^b	3.7
6	3-Me	94	3.9
7	3-Cl	84	3.10
8	3-CF ₃	60	3.11
9	3-NO ₂	50 ^b	3.12
10	4-Me	65	3.13
11	4-F	78	3.14
12	4-Cl	87	3.15
13	4-tBu	85	3.16
14	4-MeO	70	3.17
15	4-CO ₂ Me	33 (74) ^c	3.18
16	4-CN	0 ^b (0) ^{b,c}	-
17	4-NO ₂	0 ^b (0) ^{b,c}	-
18	3,4-(CH ₂) ₃	74	3.19

^aConditions: Aniline (3 mmol), 1,4-butanediol (3.3 mmol), [Ru(*p*-cymene)Cl₂]₂ (2.5 mol%), DPEphos (5 mol%), Et₃N (10 mol%), toluene (3 mL), reflux, 24 h; ^bConversion determined by ¹H NMR;

^cValue in parentheses run in *p*-xylene, 155 °C, 24 h.

Table 2 - Aniline Screen

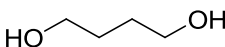
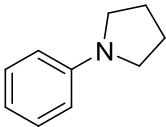
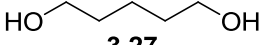
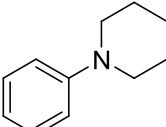
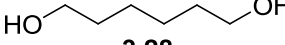
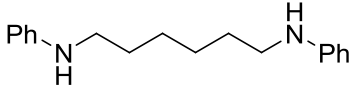
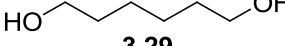
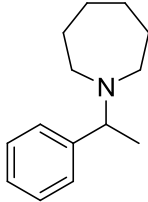
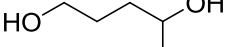
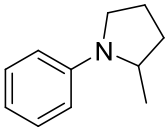
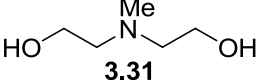
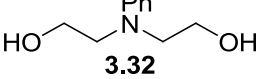
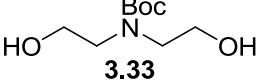
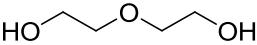
Having established that a wide range of aromatic amines could be tolerated, we wanted to expand the substrate scope to non-aromatic primary amines and heterocycles (Table 3). The results of both benzylamine (Entry 1, Table 3) and 2-phenethylamine (Entry 2, Table 3) were very similar, however, an increased yield was obtained with an α -branched amine (Entry 3, Table 3), again illustrating the previous conclusion that the result is driven by the nucleophilicity of the amine. It was also pleasing to see that an enantiopure amine (Entry 4, Table 3) could be used without racemisation of the chiral centre occurring. The inclusion of heterocycles was also tolerated, with furfurylamine (Entry 5, Table 3) resulting in a reasonable yield, while the pyridylamines (Entries 6-8, Table 3) conformed to the pattern previously seen with the anilines. While this work was underway, the group was successful at mono-alkylating sulphonamides¹³; accordingly we applied similar conditions to affect dialkylation, without any success (Entry 9, Table 3).

Entry ^a	Amine	Isolated Yield (%)	Product
1		72	3.20
2		69	3.21
3		82	3.22
4 ^b		82	3.23
5		63	3.24
6		26 ^c	3.25
7		58	3.26
8		0 ^c	-
9		0 ^c (0) ^{c,d}	-

^aConditions: Amine (3 mmol), 1,4-butanediol (3.3 mmol), [Ru(*p*-cymene)Cl₂]₂ (2.5 mol%), DPEphos (5 mol%), Et₃N (10 mol%), toluene (3 mL), reflux, 24 h; ^b>95% *e.e.* determined by ¹H NMR using a chiral shift reagent and comparison of specific rotation to literature references²⁴; ^cConversion determined by ¹H NMR; ^dValue in parentheses run in *p*-xylene, 155 °C, 24 h.

Table 3 - Non-Aromatic Primary Amines and Heterocycles

With a wide range of amines tolerated, we turned our attention to varying the diol component of the reaction. A range of diols was screened, with varying chain lengths and some containing heteroatoms (Table 4).

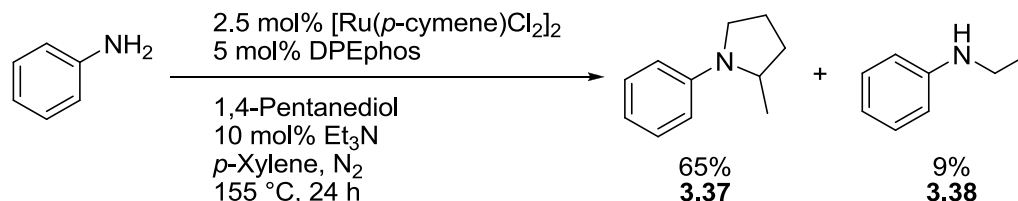
Entry ^a	Diol	Result	Isolated Yield (%)
1	 3.27	 3.3	78
2	 3.27	 3.2	72
3 ^b	 3.28	 3.35	55
4 ^c	 3.29	 3.36	65
5 ^d	 3.30	 3.37	65
6	 3.31	No Reaction	0 ^e
7	 3.32	No Reaction	0 ^e
8	 3.33	No Reaction	0 ^e
9	 3.34	No Reaction	0 ^e

^a Conditions: Aniline (3 mmol), diol (3.3 mmol), [Ru(*p*-cymene)Cl₂]₂ (2.5 mol%), DPEphos (5 mol%), Et₃N (10 mol%), toluene (3 mL), reflux, 24 h; ^b Diol (3 mmol), aniline (6.6 mmol); ^c α -Methylbenzylamine used instead of aniline; ^d Run in *p*-xylene at 155 °C, 24 h; ^e Conversion determined by ¹H NMR.

Table 4 - Diol Tolerance

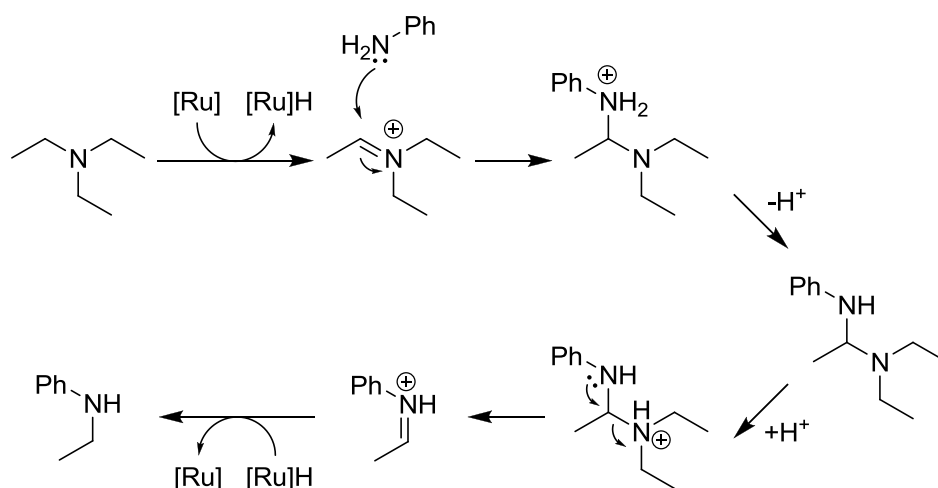
The reaction of 1,4-pentanediol (**3.30**) proceeded smoothly at a higher temperature (155 °C) using *p*-xylene as the solvent, showing complete consumption of the aniline. The increase in temperature corresponds to the conditions used for the coupling of

secondary amines with secondary alcohols¹³ which had been reported. When purifying the product, two chromophores were detected by UV analysis of the TLC, both were isolated and analysed. The major product was the desired cyclic pyrrolidine (**3.37**), the minor product was *N*-ethylaniline (**3.38**) (Scheme 5).



Scheme 5 - Reaction of 1,4-Pentandiol at 155 °C

Formation of the by-product can be attributed to transfer of an ethyl group from the catalytic triethylamine present in the reaction mixture. At the increased temperature, the catalyst is able to perform borrowing hydrogen reactions on tougher substrates such as sulphonamides and secondary alcohols.¹³ We reasoned that at the higher temperature oxidation of the triethylamine was occurring, followed by nucleophilic addition of the aniline to form an amination. Protonation and elimination would lead to the imine intermediate which could then be reduced using the hydrogen removed by the initial oxidation (Scheme 6).



Scheme 6 - Formation of *N*-Ethylaniline By-product

This is not the first example of this reaction; indeed both the Williams group²⁵ and others²⁶⁻³⁰ have manipulated this pathway to use amines as alkylating agents.

Finally, the inclusion of a heteroatom (Entries 6-9, Table 4) in the backbone of the diol led to no product in any case, analysis of the crude reaction mixtures by ¹H NMR

showed only starting material. The return of starting materials in these cases suggests that the active catalyst was not formed. This could be due to competitive ligand binding by the diol substrates themselves, all of which have a 1,4,7-substitution pattern of heteroatoms which can act as bi- or tri-dentate ligands, as illustrated in the literature.³¹⁻³²

3.4 CHAPTER SUMMARY

- An improved catalytic system has been developed for the formation of cyclic tertiary amines using a previously known catalyst.
- The reaction will tolerate a wide range of substrates and the results can be predicted by consideration of the electron density at the nitrogen lone pair.
- The reaction will tolerate α -stereocentres on the amine without erosion of the enantiomeric excess.
- The reaction is unsuccessful at forming 6-membered cyclic rings containing more than one heteroatom.

3.5 References

- [1] Hamid, M. H. S. A.; Williams, J. M. J. *Tetrahedron Lett.* **2007**, 48, 8263-8265.
- [2] He, J.; Kim, J. W.; Yamaguchi, K.; Mizuno, N. *Angew. Chem. Int. Ed.* **2009**, 48, 9888-9891.
- [3] Kawahara, R.; Fujita, K.; Yamaguchi, R. *J. Am. Chem. Soc.* **2010**, 132, 15108-15111.
- [4] Yamaguchi, R.; Mingwen, Z.; Kawagoe, S.; Asai, C.; Fujita, K. *Synthesis* **2009**, 7, 1220-1223.
- [5] Yamaguchi, R.; Kawagoe, S.; Asai, C.; Fujita, K. *Org. Lett.* **2008**, 10, 181-184.
- [6] Del Zotto, A.; Baratta, W.; Sandri, M.; Verardo, G.; Rigo, P. *Eur. J. Inorg. Chem.* **2004**, 524-529.
- [7] Bähn, S.; Tillack, A.; Imm, S.; Mevius, K.; Michalik, D.; Hollmann, D.; Neubert, L.; Beller, M. *ChemSusChem* **2009**, 2, 551-557.
- [8] Fujita, K.; Enoki, Y.; Yamaguchi, R. *Tetrahedron* **2008**, 64, 1943-1954.
- [9] Tillack, A.; Hollmann, D.; Mevius, K.; Michalik, D.; Bähn, S.; Beller, M. *Eur. J. Org. Chem.* **2008**, 4745-4750.
- [10] Hamid, M. H. S. A.; Williams, J. M. J. *Tetrahedron Lett.* **2007**, 48, 8263-8265.
- [11] Ganguly, S.; Joslin, F. L.; Roundhill, D. M. *Inorg. Chem.* **1989**, 28, 4564-4565.
- [12] Murahashi, S.-I.; Kondo, K.; Hakata, T. *Tetrahedron Lett.* **1982**, 23, 229-232.
- [13] Hamid, M. H. S. A.; Allen, C. L.; Lamb, G. W.; Maxwell, A. C.; Maytum, H. C.; Watson, A. J. A.; Williams, J. M. J. *J. Am. Chem. Soc.* **2009**, 131, 1766-1774.
- [14] Grigg, R.; Mitchell, T. R. B.; Sutthivaiyakit, S.; Tongpenyai, N. *J. Chem. Soc. Chem. Commun.* **1981**, 611-612.

- [15] Saidi, O.; Blacker, A. J.; Lamb, G. W.; Marsden, S. P.; Taylor, J. E.; Williams, J. M. J. *Org. Process Res. Dev.* **2010**, *14*, 1046-1049.
- [16] Tsuji, Y.; Huh, K.-T.; Ohsugi, Y.; Watanabe, Y. *J. Org. Chem.* **1985**, *50*, 1365-1370.
- [17] Fujita, K.; Fujii, T.; Yamaguchi, R. *Org. Lett.* **2004**, *6*, 3525-3528.
- [18] Abbenhuis, R. A. T. M.; Boersma, J.; van Koten, G. *J. Org. Chem.* **1998**, *63*, 4282-4290.
- [19] Hamid, H. M. S. A.; Williams, J. M. J. *Chem. Commun.* **2007**, 725-727.
- [20] Maytum, H. C.; Tavassoli, B.; Williams, J. M. J. *Org. Lett.* **2007**, *9*, 4387-4389.
- [21] Ishii, Y.; Osakada, K.; Ikariya, T.; Saburi, M.; Yoshikawa, S. *J. Org. Chem.* **1986**, *51*, 2034-2039.
- [22] Murahashi, S.-I.; Ito, K.; Naota, T.; Maeda, Y. *Tetrahedron Lett.* **1981**, *22*, 5327-5330.
- [23] Zhao, J.; Hartwig, J. F. *Organometallics* **2005**, *24*, 2441-2446.
- [24] Sugiyama, S.; Morishita, K.; Chiba, M.; Ishii, K. *Heterocycles* **2002**, *57*, 637-648.
- [25] Saidi, O.; Blacker, A. J.; Farah, M. M.; Marsden, S. P.; Williams, J. M. J. *Angew. Chem. Int. Ed.* **2009**, *48*, 7375-7378.
- [26] Hollmann, D.; Bähn, S.; Tillack, A.; Beller, M. *Angew. Chem. Int. Ed.* **2007**, *46*, 8291-8294.
- [27] Hollmann, D.; Bähn, S.; Tillack, A.; Parton, R.; Altink R.; Beller, M. *Tetrahedron Lett.* **2008**, *49*, 5742-5745.
- [28] Hollmann, D.; Bähn, S.; Tillack, A.; Beller, M. *Chem. Commun.* **2008**, 3199-3201.
- [29] Bähn, S.; Hollmann, D.; Tillack, A.; Beller, M. *Adv. Synth. Catal.* **2008**, *350*, 2099-2103.
- [30] Lorentz-Petersen, L. L. R.; Jensen, P.; Madsen, R. *Synthesis* **2009**, *24*, 4110-4112.

- [31] Hong, Y.; Mun, S.-D.; Lee, J.; Do, Y.; Kim, Y. *J. Organomet. Chem.* **2008**, 693, 1945-1951.
- [32] Bo, C.; Fandos, R.; Feliz, M.; Hernández, C.; Otero, A.; Rodríguez, A.; Ruiz, M. J.; Pastor, C. *Organometallics* **2006**, 25, 3336-3344.

4 RESULTS AND DISCUSSION III

4.1 Background

The combination of $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$ and DPEphos has been proven to be a versatile catalyst able to form a wide variety of C-N bonds *via* the borrowing hydrogen approach and the Williams group has exploited this reactivity.¹ However, most of the reactions require long reaction times and high temperatures. Kempe and co-workers have developed a P-N ligand that when combined with a suitable iridium source facilitated C-N bond formation under milder conditions.^{2,3} We wished to develop a catalyst or suitable reaction conditions to allow C-N bond formation to occur more quickly than previously reported.

4.2 Initial Studies

Initial work focused on developing a stable preformed catalyst that could become commercially available.

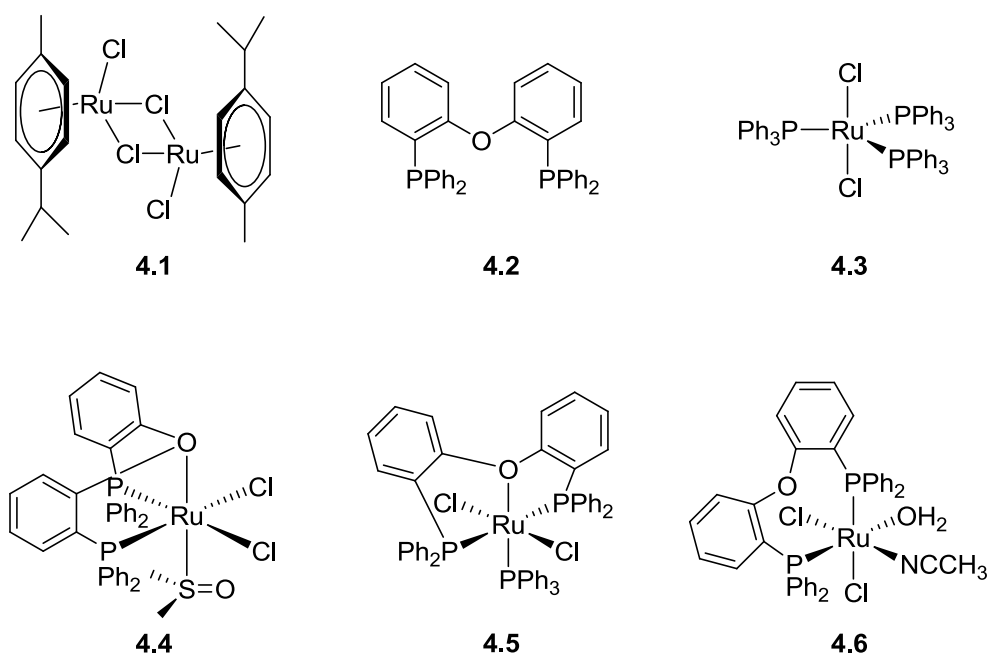
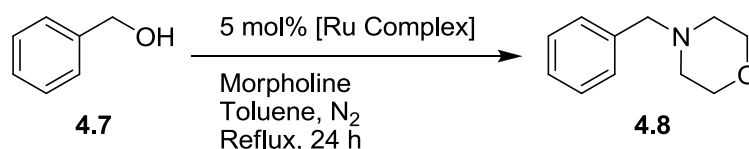


Figure 1 - Ruthenium Based Catalysts & Ligands

The combination of $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$ (**4.1**) and DPEphos (**4.2**) has been already been shown by the Williams group to be an active system as mentioned above, in addition the combination of $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$ (**4.1**) and triphenylphosphine has been shown to be active for C-N bond formation with sulfonamides at higher

temperatures.⁴ A search of the literature revealed several complexes containing ruthenium/DPEphos combinations.⁵ These were all synthesized successfully following the literature procedures except $[\text{RuCl}_2(\text{DPEphos})(\text{CH}_3\text{CN})(\text{H}_2\text{O})]$ (**4.6**) which despite repeated attempts was unsuccessful. These were then tested under standard reaction conditions (Scheme 1).



Scheme 1 - Standard Reaction Conditions

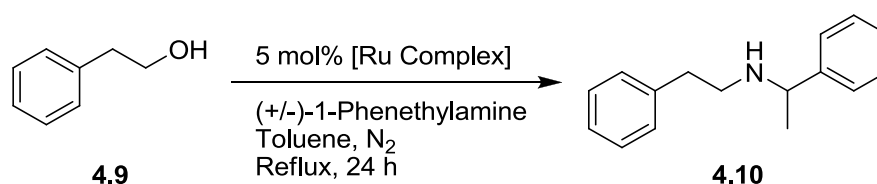
Entry ^a	Catalyst	Conversion (%) ^b
1	4.1/4.2	100
2	4.1/4.2 / PPh_3	98 ^c
3	4.3	96
4	4.4	94
5	4.5	97

^aConditions: Benzyl alcohol (1 mmol), morpholine (1 mmol), [Ru] (5 mol% with respect to ruthenium), ligand (5 mol%), toluene (1 mL), reflux, 24 h;

^bConversion determined by ^1H NMR; ^c5 mol% PPh_3

Table 1 - Tertiary Amine Formation Catalyst Screen

Analysis of the crude reaction mixtures by ^1H NMR showed good conversions for all catalyst combinations. However, the catalyst loading for this reaction was double the reported loading,⁶ but despite this, these results were encouraging.



Scheme 2 - Secondary Amine Reaction Conditions

Having established that a range of ruthenium/DPEphos combinations was active for the synthesis of tertiary amines from secondary amines, we next wanted to test them in the more challenging synthesis of secondary amines using primary amines (Scheme 2, Table 2).

Entry ^a	Catalyst	Conversion (%) ^b
1	4.1/4.2	100
2	4.1/4.2 /PPh ₃	100 ^c
3	4.3	49
4	4.4	100
5	4.5	0

^aConditions: Benzyl alcohol (1 mmol), (+/-)-1-phenethylamine (1 mmol), [Ru] (5 mol% with respect to ruthenium), toluene (1 mL), reflux, 24 h;

^bConversion determined by ¹H NMR; ^c5 mol% PPh₃

Table 2 - Secondary Amine Formation Catalyst Screen

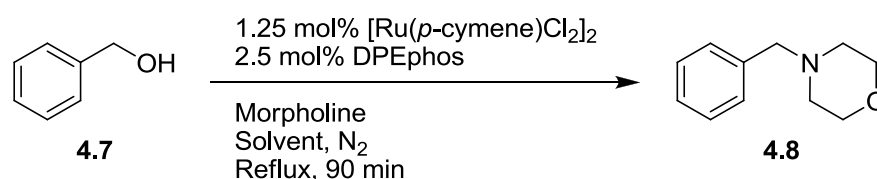
The results of this screen were more interesting. The inclusion of triphenylphosphine into the reaction mixture (Entry 2, Table 2) showed little or no difference in conversion compared to the reaction without triphenylphosphine (Entry 1, Table 2). However, when the pre-formed catalyst with the triphenylphosphine already bound [RuCl₂(DPEphos)(PPh₃)] (**4.5**) (Entry 5, Table 2) was used there was no conversion to product. Comparison of these results with the reaction of [RuCl₂(dmsO)(DPEphos)] (**4.4**) (Entry 4, Table 2) and RuCl₂(PPh₃)₃ (**4.3**) (Entry 3, Table 2) can start to shed some light on the active species.

Both RuCl₂(PPh₃)₃ (**4.3**) and [RuCl₂(DPEphos)(PPh₃)] (**4.5**) have triphenylphosphine bound, however, only reactions using RuCl₂(PPh₃)₃ (**4.3**) showed any conversion. The difference between the two catalysts is the latter has the triphenylphosphine bound in the axial position, although it is unlikely that this will have any affect as it is well known that triphenylphosphine can dissociate from the metal, and this is required for RuCl₂(PPh₃)₃ (**4.3**) to form an active catalyst and facilitate the reaction.

Comparison of [RuCl₂(dmsO)(DPEphos)] (**4.4**) and [RuCl₂(DPEphos)(PPh₃)] (**4.5**) again shows that the latter catalyst shows no activity while the first shows excellent activity. As mentioned previously, dissociation of the triphenylphosphine is likely, so the difference in reactivity can be attributed to the binding of the DPEphos ligand. In the [RuCl₂(dmsO)(DPEphos)] (**4.4**) complex, the two phosphines are bound in cis equatorial positions with the oxygen binding through an axial position. Alternatively, [RuCl₂(DPEphos)(PPh₃)] (**4.5**) has the DPEphos bound in a plane with 180° between the two phosphines and 90° between each phosphine and the oxygen. The resulting difference between the two catalysts is that [RuCl₂(dmsO)(DPEphos)] (**4.4**) can form two free equatorial sites with loss of the chlorines, while [RuCl₂(DPEphos)(PPh₃)] cannot. It is worth noting that both catalysts can form two free sites in an axial-

equatorial relationship. This implies that the active species for secondary amine formation requires two free equatorial sites, whilst the active species for tertiary amine only requires one.

From the screen it is clear that in our pursuit for a stable preformed catalyst that the $[\text{RuCl}_2(\text{dmsO})(\text{DPEphos})]$ (**4.4**) is the lead candidate. However, analysis of the synthesis⁵ of this catalyst starts from $\text{RuCl}_2(\text{dmsO})_4$ (**4.11**) which is far more expensive than $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$ (**4.1**), nor is the synthesis of this precursor from RuCl_3 particularly appealing.⁷ Added to this is the long-term stability of the dmsO remaining bound to the catalyst on storage means that this route to an improved catalytic system is unlikely.



Scheme 3 - Model Reaction Conditions for Ionic Liquid Screen

Entry ^a	Solvent	Conversion (%) ^b
1	Toluene	18
2	[BMIM][PF ₆]	34
3	[BMIM][Cl]	4
4	[BMIM][OTf]	14
5	[BMIM][BF ₄]	31
6	[BMIM][SbF ₆]	18
7	[BDMIM][PF ₆]	24
8	[BMIM][PF ₆]	61 ^c

^aConditions: Benzyl alcohol (1 mmol), morpholine (1 mmol), $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$ (1.25 mol%), DPEphos (2.5 mol%), solvent (1 mL), 115 °C, 90 min; ^bConversion determined by ¹H NMR; ^cReaction heated for 6 h.

Table 3 - Ionic Liquid Screen

The choice of solvent can have a large impact on the course of a reaction.⁸ The Williams group,⁹ Yamaguchi and co-workers¹⁰⁻¹¹ and the Madsen group¹² have all shown that iridium catalysed borrowing hydrogen reactions can occur on or in water, whilst Milstein and Gunanathan¹³ have demonstrated that ruthenium can also catalyse reactions on or in water. Further work by the Williams group has also shown unique reactivity of iridium catalysed borrowing hydrogen reactions in ionic liquids.¹⁴

However, there were no published reports of ruthenium catalysed borrowing hydrogen reactions in ionic liquids and considering the published work with iridium, we hoped to see similar acceleration of the reaction to shorten reaction times (Scheme 3).

Initial work focused on a screen of ionic liquids with comparison to toluene over 90 min (Table 3).

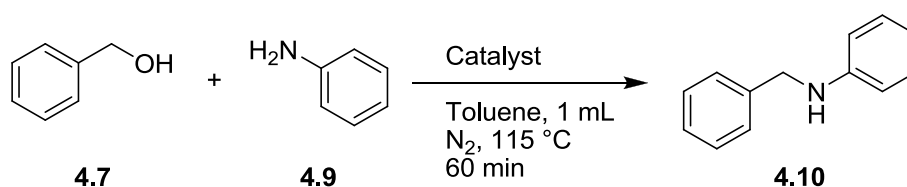
Initial results from the screen looked very promising, showing that [BMIM][PF₆] (Entry 2, Table 3) had almost doubled the conversion compared with toluene (Entry 1, Table 3). Furthermore, the ionic liquid acting as a carbene ligand can also be ruled out due to the increased conversion also illustrated by [BDMIM][PF₆] (Entry 7, Table 7) which is unable to form a carbene due to the blocking methyl group. However, on extended heating, the rate of reaction was not maintained (Entry 8, Table 3). The effect of catalyst loading and reaction time were then investigated (Table 4).

Entry ^a	Solvent	Catalyst Loading (Mol%) ^b	Time (h)	Conversion ^c
1	[BMIM][PF ₆]	5	6	94
2	[BMIM][PF ₆]	4	6	99
3	[BMIM][PF ₆]	3	6	90
4	[BMIM][PF ₆]	4	5	94
5	[BMIM][PF ₆]	4	4	91
6	Toluene	4	4	99

^aConditions: Benzyl alcohol (1 mmol), morpholine (1 mmol), [Ru(*p*-cymene)Cl₂]₂, DPEphos, solvent (1 mL), 115 °C; ^bWith respect to [Ru]; ^cConversion determined by ¹H NMR.

Table 4 - Time and Catalyst Loading Screen

Further analysis of the use of ionic liquids was disappointing, demonstrating that a higher catalyst loading of 4 mol% was required to reach full conversion in 6 hours (Entry 2, Table 4). Decreasing the reaction time whilst maintaining the high conversion was possible at the higher catalyst loading (Entry 4 & 5, Table 4) however, the results were not as good when compared with toluene (Entry 6, Table 4). Furthermore, other C-N bond forming reactions either stalled or were not active in the ionic liquid, illustrating poor reaction scope and ending this line of investigation.

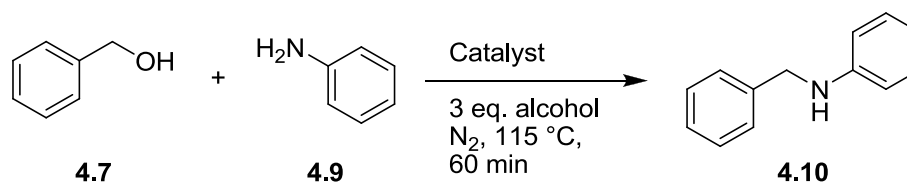
**Scheme 4 - Initial Microwave Screening Conditions**

Entry ^a	Solvent	Conversion (%) ^b
1	Toluene	0
2	Dioxane	>5
3	DME	>5
4	<i>t</i> -BuOH	>5
5	MeOH	0
6	H ₂ O	0

^aConditions: Benzyl alcohol (1 mmol), aniline (1 mmol), [Ru(*p*-cymene)Cl₂]₂ (2.5 mol%), DPEphos (5 mol%), solvent (1 mL), 115 °C, 60 min; ^bConversion determined by ¹H NMR.

Table 5 - Microwave Solvent Screen

Grigg and co-workers have shown that the use of microwaves can accelerate iridium catalysed borrowing hydrogen reactions¹⁵⁻¹⁷ however; there was no precedent for the use of ruthenium under these conditions, nor the application to C-N bond formation. As such, a set of standard conditions were chosen (Scheme 4) and the three major catalyst systems published by Yamaguchi,¹⁸ Beller¹⁹ and Williams¹ were tested at their reported loadings.

**Scheme 5 - Revised Microwave Conditions**

Under the conditions chosen, only the iridium system published by Yamaguchi showed any activity (7% conversion by ¹H NMR). Continuing to work with the catalyst system published by the Williams group, a screen of oxygen containing solvents was conducted to see if altering the solvent would have any beneficial effects on the reaction (Table 5).

The results did not show any increase in conversion. A review of the conditions used by Grigg and co-workers revealed that they used no solvent in their reactions, but an excess of alcohol instead. With this information, a modified set of conditions was screened (Scheme 5).

Using the revised conditions both the catalyst systems used by Yamaguchi and the Williams group were successful giving 100% and 52% conversions respectively. The catalyst system used by Beller and co-workers¹⁶ gave no conversion. Despite the full conversion with the $[\text{IrCp}^*\text{Cl}_2]_2$ catalyst, we chose to continue our work with the $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2/\text{DPEphos}$ system as it has been successfully used previously by the Williams group.¹ Further optimisation was conducted to find the optimal reaction conditions.

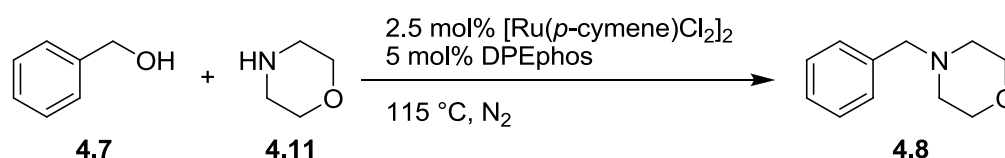
Entry ^a	Equivalents of Alcohol	Time (min)	Conversion (%) ^b
1	3	60	52
2	3	120	100
3	2	120	88
4	1	120	71
5	3 ^c	120	60
6	3 ^c	240	100

^aConditions: Benzyl alcohol, aniline (1 mmol), $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$ (2.5 mol%), DPEphos (5 mol%), solvent (1 mL), 115 °C, 60 min; ^bConversion determined by ¹H NMR; ^cEquivalents of amine.

Table 6 - Optimisation of Conditions

By increasing the reaction time (Entry 2, Table 6) it was possible to push the reaction to full conversion. However, decreasing the amount of alcohol led to a decrease in conversion (Entry 3 & 4, Table 6), even on extended heating the conversion did not increase. It was also possible to use an excess of amine (Entry 5, Table 6), although this required doubling the reaction time (240 min, Entry 6, Table 6).

Having established suitable reaction conditions for the reaction of aniline (**4.9**), the reaction of morpholine (**4.11**) with benzyl alcohol (Scheme 6) was evaluated.

**Scheme 6 - Reaction of Morpholine with Benzyl Alcohol**

Entry ^a	Equivalents of Alcohol	Time (min)	Conversion (%) ^b
1	3	60	100
2	2	60	100
3	1.6	90	100
4	1.2	90	94
5	1.2	120	94
6	1.6	90	100 ^c

^aConditions: Benzyl alcohol (1 mmol), morpholine (1 mmol), [Ru(*p*-cymene)Cl₂]₂ (2.5 mol%), DPEphos (5 mol%), 115 °C; ^bConversion determined by ¹H NMR; ^cReaction scaled to 3 mmol.

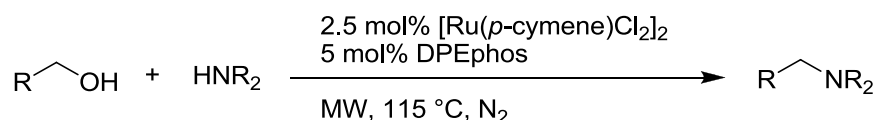
Table 7 - Reaction with Morpholine

The initial test (Entry 1, Table 7) gave full conversion to the product and it was then possible to reduce the excess of alcohol down to 1.6 equivalents (Entry 3, Table 7) without hampering the conversion. However, on reducing the excess further (Entry 4, Table 7), it was not possible to drive the reaction to completion even on extended heating (Entry 5, Table 7). It was also possible to increase the reaction scale whilst still maintaining the short reaction time (Entry 6, Table 7).

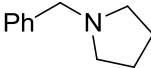
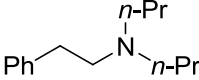
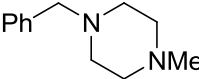
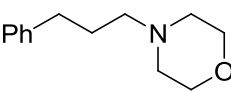
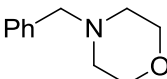
3.3 Reaction Scope

Having established a set of conditions, a variety of secondary amines and primary alcohols were coupled to evaluate the scope of the reaction (Scheme 7 & Table 8).

We were pleased to see that all the products could be isolated in high yields comparable with thermal heating¹ but with the desired shorter reaction times. The use of excess amine instead of alcohol (Entry 2, Table 8) was also possible and added value to the reaction as this meant the least expensive coupling partner, whichever it may be, could be used in excess while still giving good yields. Although the reactions proceeded well, an increase in temperature (125 °C) was required for the acyclic substrate (**4.13**) to couple in high yield.



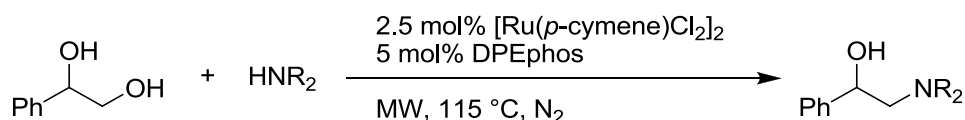
Scheme 7 - Tertiary Amine Synthesis

Entry ^a	Product	Equivalents of Alcohol	Time (min)	Isolated Yield (%)
1	 4.12	1.6	90	79
2	 4.13	2.0 ^b	90	94 ^c
3	 4.14	1.6	120	79
4	 4.15	1.6	90	83
5	 4.8	1.6	90	81

^aConditions: Amine (3 mmol), alcohol, [Ru(*p*-cymene)Cl₂]₂ (2.5 mol%), DPEphos (5 mol%), 115 °C; ^bEquivalents of amine; ^c125 °C.

Table 8 - Tertiary Amine Results

Thermal C-N bond formation *via* borrowing hydrogen has been shown to react selectively at the primary¹ or least hindered alcohol.²⁰ We wished to determine if this was still the case with microwave heating. To test this, morpholine was then reacted with a series of 1,2-diols, however, only diols with a benzylic secondary alcohol were active towards coupling. The use of alkyl 1,2-diols led to the oxidation of the secondary alcohol to the corresponding hydroxy ketone. This is in contrast to previously reported thermal coupling reactions, suggesting that there may be limitations to the use of microwave heating in specific cases. With the limitation of the 1,2-diol substrate evaluated, various secondary amines were screened against 1-phenyl-1,2-ethanediol²⁰ (Scheme 8, Table 9).



Scheme 8 - Amino-alcohol Synthesis

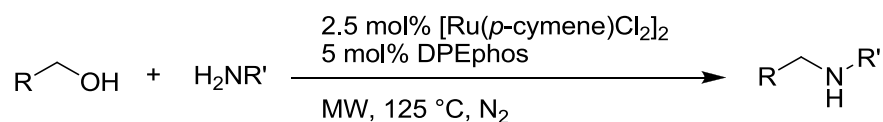
Entry ^a	Product	Equivalents of Amine	Time (min)	Isolated Yield (%)
1	 4.16	2.0	90	75
2	 4.17	2.0	90	90
3	 4.18	2.0	90	65
4	 4.19	2.0	120	79
5	 4.20	2.0	90	61

^aConditions: Diol (1 mmol), amine (2 mmol), [Ru(*p*-cymene)Cl₂]₂ (2.5 mol%), DPEphos (5 mol%), 115 °C.

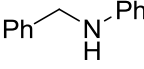
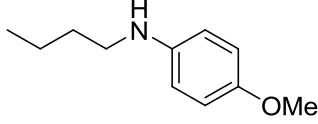
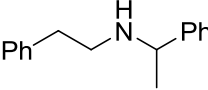
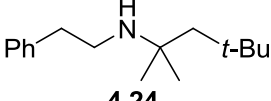
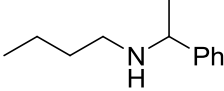
Table 9 - Amino-alcohol Results

Again the yields for most substrates were good (Entries 1, 2 & 4, Table 9), however, the introduction of acyclic amine (**4.20**) or a larger cyclic amine (**4.18**) gave full conversion by ¹H NMR despite the lower isolated yield.

We then turned our attention to the coupling of primary amines, which under the previous conditions gave poor conversion. We assumed this was due to the deactivation of the catalyst as a result of the amine binding more tightly to the catalyst under the concentrated conditions.²¹ Assuming this to be the case, the reaction temperature was increased by 10 °C, and the reaction progressed to full conversion. With the new conditions established, a series of primary amines was coupled to evaluate the scope of the reaction (Scheme 9 & Table 10).



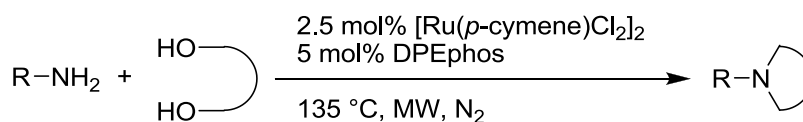
Scheme 9 - Secondary Amine Synthesis

Entry ^a	Product	Equivalents of Alcohol	Time (min)	Isolated Yield (%)
1	 4.21	3.0	120	91 ^b
2	 4.22	2.1	120	73 ^b
3	 4.23	1.6	60	94
4	 4.24	2.0	90	82
5	 4.25	1.6	60	80

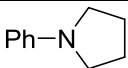
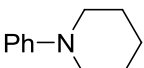
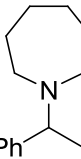
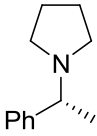
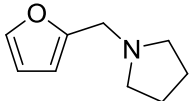
^aConditions: Amine (1 mmol), alcohol, [Ru(*p*-cymene)Cl₂]₂ (2.5 mol%), DPEphos (5 mol%), 125 °C; ^b115 °C.

Table 10 - Secondary Amine Results

As expected, the results were good, with a range of alcohols and amines coupling in high yields. Anilines (Entries 1 & 2, Table 10) also gave good results at lower temperatures (115 °C) as shown in the initial work. The lower temperature of these reactions can be attributed to the lone pair on the nitrogen being less nucleophilic due to the orbital overlap with the aromatic ring. As a result the nitrogen will bind less tightly to the catalyst, reducing the amount of deactivation. Bulky amines (Entries 3-5, Table 10) also coupled well and again gave yields comparable with thermal heating.



Scheme 10 - Cyclic Tertiary Amine Synthesis

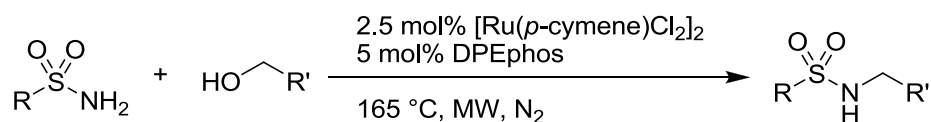
Entry ^a	Product	Equivalents of Alcohol	Time (min)	Isolated Yield (%)
1	 4.26	1.6	90	88
2	 4.27	1.6	90	81
3	 4.28	1.6	90	77
4	 4.29	1.6	90	82
5	 4.30	1.6	90	54

^aConditions: Amine (1 mmol), diol (1.6 mmol), [Ru(*p*-cymene)Cl₂]₂ (2.5 mol%), DPEphos (5 mol%), 135 °C.

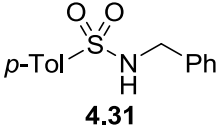
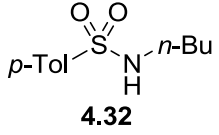
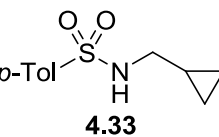
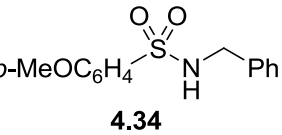
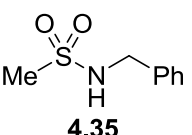
Table 11 - Cyclic Tertiary Amine Results

Having determined that mono-alkylation of primary amines was possible, we wanted to see if we could repeat some of our earlier work (Chapter 3) and di-alkylate using symmetric diols (Scheme 10).^{1, 22-23}

Again, a slight increase in temperature (135 °C) was required for the reaction to proceed to completion. With the conditions established, a range of substrates were screened (Table 11) giving generally good yields, comparable with our previously reported results. The only exception was furfurylamine (**4.30**), which gave a lower yield. When an enantiomerically enriched amine (**4.29**) was alkylated, again, no racemisation was observed, proven by ¹H NMR using a chiral shift reagent²⁴⁻²⁵ and comparison of the specific rotation with a literature reference.²⁶



Scheme 11 - Sulfonamide Alkylation

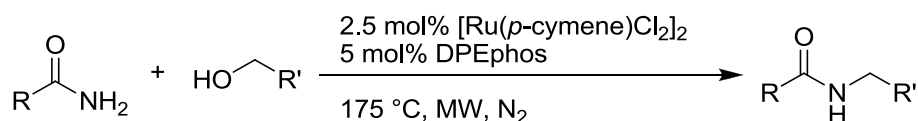
Entry ^a	Product	Equivalents of Alcohol	Time (min)	Isolated Yield (%)
1	 <p>4.31</p>	3.0	120	91
2	 <p>4.32</p>	3.0	180	96
3	 <p>4.33</p>	3.0	180	74
4	 <p>4.34</p>	3.0	180	91
5	 <p>4.35</p>	3.0	180	86

^aConditions: Amide (1 mmol), alcohol (3 mmol), [Ru(*p*-cymene)Cl₂]₂ (2.5 mol%), DPEphos (5 mol%), 165 °C.

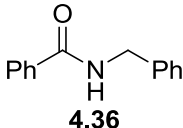
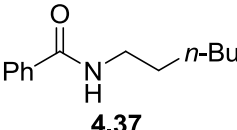
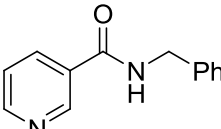
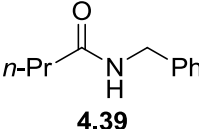
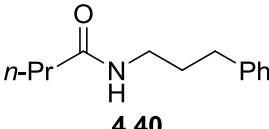
Table 12 - Sulfonamide Alkylation Results

Having screened a series of different amine and alcohol couplings, we turned our attention towards the alkylation of sulfonamides.^{1,4,27} An increase in temperature (165 °C) and reaction time (180 min) was required to drive the reaction to completion. An increased amount of alcohol was also necessary; we assumed this was required to dissolve the sulfonamide. However, contrary to previous reports, the inclusion of an inorganic base to deprotonate the sulfonamide was not required. The results of the sulfonamide couplings (Table 12) were good, with high yields except for

cyclopropylmethanol (**4.33**). In this case the yield was low due to the alcohol undergoing oxidative dimerization to form the symmetric ester.²⁸⁻³²



Scheme 12 - Alkylation of Primary Amides

Entry ^a	Product	Equivalents of Alcohol	Time (min)	Isolated Yield (%)
1	 4.36	3.0	120	66
2	 4.37	3.0	120	72
3	 4.38	3.0	180	54 ^b
4	 4.39	3.0	120	74
5	 4.40	3.0	120	79

^aConditions: Amide (1 mmol), alcohol (3 mmol), [Ru(*p*-cymene)Cl₂]₂ (2.5 mol%), DPEphos (5 mol%), 175 °C; ^bConversion determined by ¹H NMR was 84%, the low yield is due to difficulties in isolation.

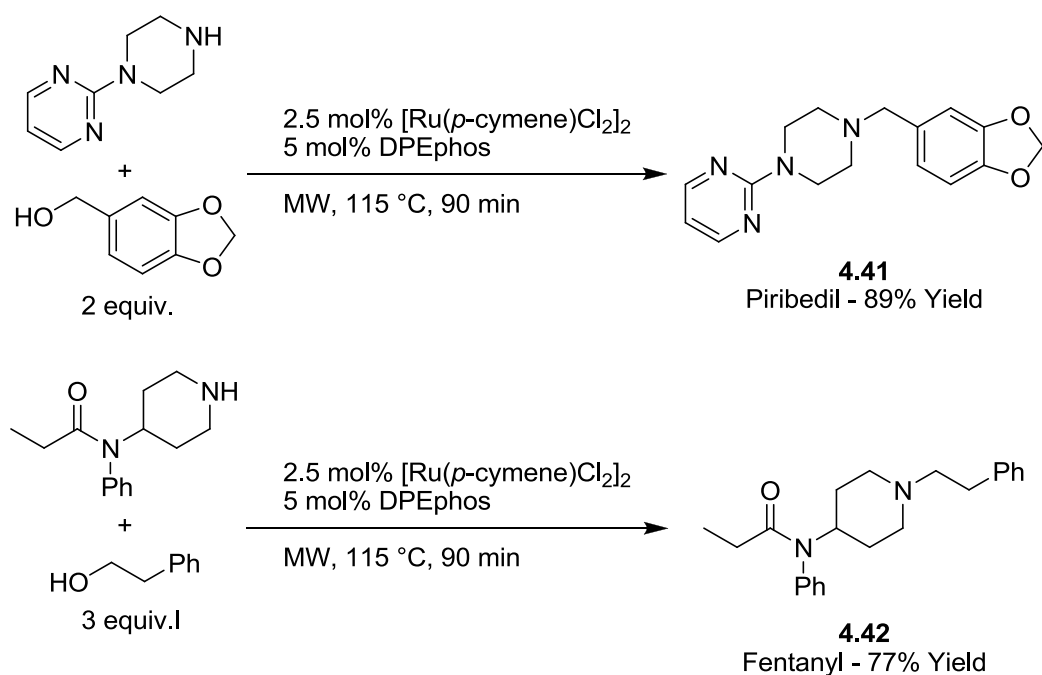
Table 13 - Alkylation of Primary Amides Results

Satisfied that we could replicate the previous results and couplings, we wanted to extend the scope of the catalyst and alkylate primary amides in the same way. This catalyst system has previously been unsuccessful in this area although there are at least three reports in the literature³³⁻³⁵ of this coupling being achieved with both ruthenium and iridium, but with high reaction temperatures. By starting with the sulfonamide conditions, it was quickly determined that the coupling of primary

amides and alcohols was possible, although to reach full conversion the reaction temperature had to be increased to 175 °C.

Despite the high reaction temperature, the reaction time was shorter than the coupling of sulfonamides (120 vs 180 min) and once again the coupling proceeded without the need for a base. The reaction scope was then evaluated and compared with the system reported by Yamaguchi et al.³⁵

Both aromatic (Entries 1 & 2, Table 13) and alkyl amides (Entries 4 & 5, Table 13) were coupled with aliphatic and benzylic alcohols with reasonable yields. The coupling of alkyl amides in particular was interesting as the yields were better than those reported by Yamaguchi, even though the reaction temperature was significantly higher. Finally, we were very pleased to isolate *N*-hexylnicotinamide in reasonable yield (**4.38**), demonstrating that the reaction was also applicable to biologically relevant molecules.



Scheme 13 - Drug Molecule Synthesis

With a range of reaction conditions established, we were keen to apply our chemistry to two pharmaceutical compounds, Piribedil (**4.41**) and Fentanyl (**4.42**), both of which were isolated in good yield (Scheme 13).

4.4 CHAPTER SUMMARY

- The combination of $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$ and DPEphos has proven to be the best catalyst system for the formation of secondary and tertiary amines over the preformed combinations present in the literature.
- The use of toluene as a reaction solvent is superior to ionic liquids.
- Microwave heating can be applied to C-N bond formation *via* borrowing hydrogen methodology under solvent free conditions.
- The use of microwave heating can be applied to a wide range of amine and amide syntheses.
- The alkylation of primary amides has been achieved using the catalyst system published by the Williams group for the first time.

4.5 References

- [1] Hamid, M. H. S. A; Allen, C. L.; Lamb, G. W.; Maxwell, A. C.; Maytum, H. C.; Watson, A. J. A.; Williams, J. M. J. *J. Am. Chem. Soc.* **2009**, *131*, 1766-1774.
- [2] Blank, B.; Michlik, S.; Kempe, R. *Chem. Eur. J.* **2009**, *15*, 3790-3799.
- [3] Michlik, S.; Kempe, R. *Chem. Eur. J.* **2010**, *16*, 13193-13198.
- [4] Lamb, G. W.; Watson, A. J. A.; Jolley, K. E.; Maxwell, A. C.; Williams, J. M. J. *Tetrahedron Lett.* **2009**, *50*, 3374-3377.
- [5] Venkateswaran, R.; Mague, J. T.; Balakrishna, M. S. *Inorg. Chem.* **2007**, *46*, 809-817.
- [6] Hamid, M. H. S. A.; Williams, J. M. J. *Tetrahedron Lett.* **2007**, *48*, 8263-8265.
- [7] Vogl, E. M.; Bruckmann, J.; Kessler, M.; Krüger, C.; Haenel, M. W. *Chem. Ber.* **1997**, *130*, 1315-1319.
- [8] Watson, A. J. A.; Maxwell, A. C.; Williams, J. M. J. *Org. Lett.* **2009**, *11*, 2667-2670.
- [9] Saidi, O.; Blacker, A. J.; Farah, M. M.; Marsden, S. P.; Williams, J. M. J. *Chem. Commun.* **2010**, 1541-1543.
- [10] Kawahara, R.; Fujita, K.; Yamaguchi, R. *J. Am. Chem. Soc.* **2010**, *132*, 15108-15111.
- [11] Kawahara, R.; Fujita, K.; Yamaguchi, R. *Adv. Synth. Catal.* **2011**, *353*, 1161-1168.
- [12] Nordstrøm, L. U.; Madsen, R. *Chem. Commun.* **2007**, 5034-5036.
- [13] Gunanathan, C.; Milstein, D. *Angew. Chem. Int. Ed.* **2008**, *47*, 8661-8664.
- [14] Saidi, O.; Blacker, A. J.; Lamb, G. W.; Marsden, S. P.; Taylor, J. E.; Williams, J. M. J. *Org. Process Res. Dev.* **2010**, *14*, 1046-1049.

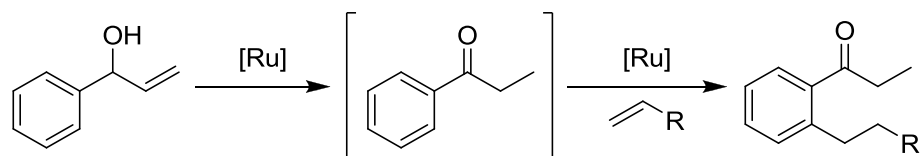
- [15] Löffberg, C.; Grigg, R.; Whittaker, M. A.; Keep, A.; Derrick, A. *J. Org. Chem.* **2006**, *71*, 8023-8027.
- [16] Löffberg, C.; Grigg, R.; Keep, A.; Derrick, A.; Sridharan, V.; Kilner, C. *Chem. Commun.* **2006**, 5000-5002.
- [17] Grigg, R.; Whitney, S.; Sridharan, V.; Keep, A.; Derrick, A. *Tetrahedron* **2009**, *65*, 4375-4383.
- [18] Fujita, K.; Yamaguchi, R. *Synlett* **2005**, *4*, 560-571.
- [19] Tillack, A.; Hollmann, D.; Michalik, D.; Beller, M. *Tetrahedron Lett.* **2006**, *47*, 8881-8885.
- [20] Bähn, S.; Tillack, A.; Imm, S.; Mevius, K.; Michalik, D.; Hollmann, D.; Neubert, L.; Beller, M. *ChemSusChem* **2009**, *2*, 551-557.
- [21] Samec, J. S. M.; Éll, A. H.; Åberg, J. B.; Privalov, T.; Eriksson, L.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **2006**, *128*, 14293-14305.
- [22] Tsuji, Y.; Huh, H.-T.; Ohsugi, Y.; Watanabe, Y. *J. Org. Chem.* **1985**, *50*, 1365-1370.
- [23] Fujita, K.; Fujii, T.; Yamaguchi, R. *Org. Lett.* **2004**, *6*, 3525-3528.
- [24] Parker, D.; Taylor, R. J. *Tetrahedron* **1987**, *43*, 5451-5456.
- [25] Parker, D. *Chem. Rev.* **1991**, *91*, 1441-1457.
- [26] Poleschner, H.; Seppelt, K. *Chem. Eur. J.* **2004**, *10*, 6565-6574.
- [27] Zhu, M.; Fujita, K.; Yamaguchi, R. *Org. Lett.* **2010**, *12*, 1336-1339.
- [28] Murahashi, S.-I.; Ito, K.; Naota, T.; Maeda, Y. *Tetrahedron Lett.* **1981**, *22*, 5327-5330.
- [29] Murahashi, S.-I.; Naota, T.; Ito, K.; Maeda, Y.; Taki, H. *J. Org. Chem.* **1987**, *52*, 4319-4327.
- [30] Suzuki, T.; Matsuo, T.; Watanabe, K.; Katoh, T. *Synlett* **2005**, *9*, 1453-1455.
- [31] Zhang, J.; Leitun, G.; Ben-David, Y.; Milstein, D. *J. Am. Chem. Soc.* **2005**, *127*, 10840-10841.

- [32] Izumi, A.; Obora, Y.; Sakaguchi, S.; Ishii, Y. *Tetrahedron Lett.* **2006**, 47, 9199-9201.
- [33] Watanabe, Y.; Ohta, T. Y. *Bull. Chem. Soc. Jpn.* **1983**, 56, 2647-2651.
- [34] Jenner, G. *J. Mol. Catal.* **1989**, 55, 241-246.
- [35] Fujita, K.; Komatsubara, A.; Yamaguchi, R. *Tetrahedron* **2009**, 65, 3624-3628.

5 RESULTS AND DISCUSSION IV

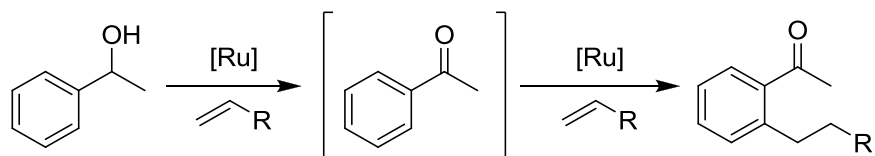
5.1 Background

In 1993 Murai reported the first catalytic applications of C-H activation of acetophenones using a ruthenium catalyst.¹ Since then, Murai and co-workers²⁻¹⁰ have fully evaluated the area providing a wealth of information which has been reviewed several times.¹¹⁻¹³ More recently Murai has been able to run the reaction at room temperature by isolating the catalytically active species.¹⁴ However, our interest focused on the recent success of using vinylic alcohols¹⁵ as starting materials. The alcohols are isomerised to the corresponding ketones which then undergo the C-H activation chemistry that has been so well reported (Scheme 1).



Scheme 1 - Tandem Isomerisation/C-H Activation Process

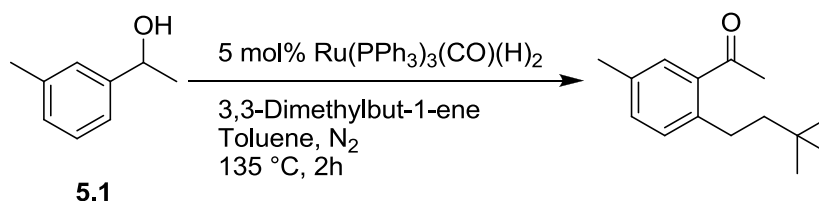
We wanted to apply a similar approach, starting from a benzyl alcohol, where the alkene would act as an oxidant and alkylating agent in a tandem oxidation/C-H activation (Scheme 2).



Scheme 2 - Proposed Work

5.2 Initial Studies

Initial work focused on applying 1-*m*-tolylethanol (**5.1**) under the reaction conditions reported by Murai.¹ We were very pleased to see that under these conditions the oxidation and alkylation proceeded. Furthermore, the alkylation occurred para to the methyl group, as expected (Scheme 3).¹⁰ It was then possible to reduce the amount of alkene from 5 equivalents down to 2.5 without hampering conversion (Entry 3, Table 1). Further reduction in the number of equivalents of alkene was possible but required an increase in the reaction time from 2 to 3 hours (Entries 5 & 6, Table 1).

**Scheme 3 - Optimisation of Equivalents of Alkene**

Entry ^a	Equivalents of Alkene	Conversion (%) ^b
1	5	100
2	3	100
3	2.5	100
4	2.2	94 ^{c,d}
5	2.2	100 ^e
6	2.1	96 ^e

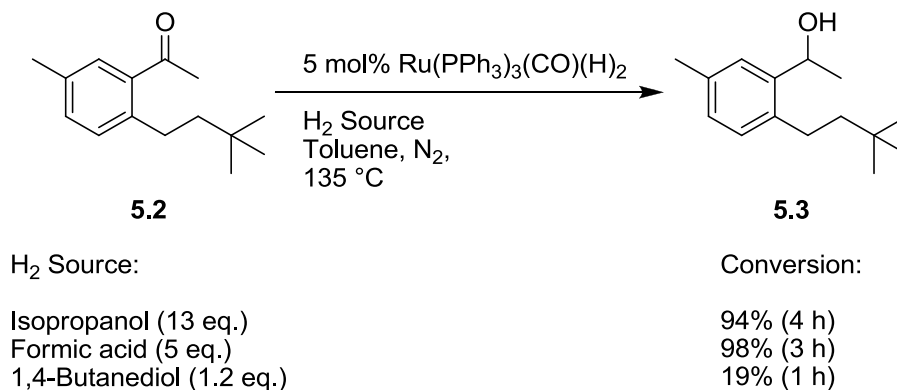
^aConditions: 1-*m*-Tolylethanol (1 mmol), 3,3-dimethylbut-1-ene, Ru(PPh₃)₃(CO)(H)₂ (5 mol%), toluene (1 mL), 135 °C, 2 h; ^bConversion determined by ¹H NMR; ^cReaction run for 2.5 h; ^dRemaining 6% was the corresponding acetophenone; ^eReaction run for 3 hours.

Table 1 - Optimisation of Equivalents of Alkene

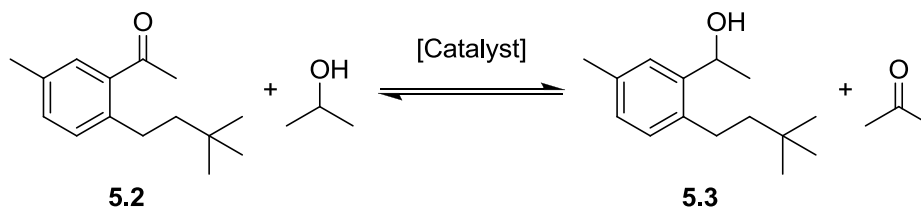
Having optimised the tandem oxidation/C-H activation we were keen to see whether the alkylated ketone could then be reduced back to the alcohol, again using ruthenium catalysed transfer hydrogenation.¹⁶ In order to test this, the tandem oxidation/C-H activation was run at 135 °C, the reaction allowed to cool to room temperature before a hydrogen source was added under nitrogen. The reaction was then re-sealed and reheated back to 135 °C, the results are summarised below (Scheme 4).

The use of isopropanol gave a favourable result (94% conversion after 4 hours), however, the use of a similar irreversible hydrogen source, 1,4-butanediol¹⁷⁻¹⁸ was poor in comparison (19% conversion after 1 hour). While the reaction times are different, extrapolation of the conversion after 1 hour would imply 76% conversion after 4 hours. The best result was obtained with formic acid (98% conversion in 3 hours), which is also an irreversible hydrogen source (the ruthenium-catalysed decomposition of formic acid is well reported¹⁹⁻²¹) generating hydrogen and carbon dioxide. Comparison of the two best results, isopropanol and formic acid, revealed formic acid as the superior hydrogen source. While isopropanol gave an excellent result under the reaction conditions, the reaction is at equilibrium (Scheme 5), as the acetone by-product formed can act as an oxidant²²⁻³⁰ to convert the alkylated alcohol

(**5.3**) back to the alkylated ketone (**5.2**). The use of a formic acid/triethylamine (5:2) mixture, previously used in reduction^{16,31-33} as an alternative to formic acid, was also tested, however, the results were not as good as those obtained with formic acid.



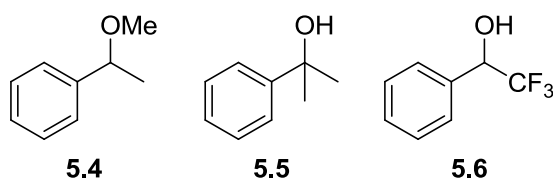
Scheme 4 - Hydrogen Source Screen



Scheme 5 - Oxidation/Reduction Equilibrium

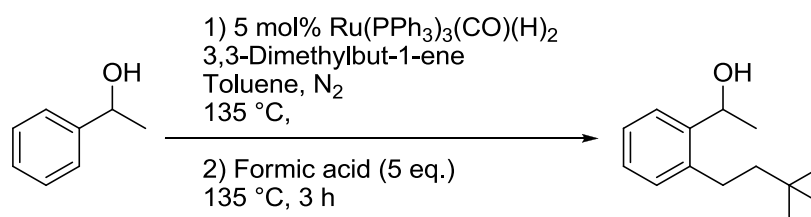
It was at this point, a question was raised about the nature of the reaction. Was the reaction sequence occurring as we had conceived? Despite the literature precedent for the ruthenium-catalysed C-H activation of acetophenones, we wanted to prove that the C-H activation was happening at the ketone oxidation state, and not at the alcohol level, which would provide evidence that our reaction was indeed occurring *via* oxidation first and C-H activation occurring second, not *vice versa* or a mixture of both pathways.

Three test substrates were devised (Figure 1). The methyl ether of 1-phenylethanol (**5.4**) and a similar tertiary alcohol (**5.5**) would offer the same oxidation level as the alcohol, whilst not being open to oxidation. The final example, α -trifluoromethyl alcohol (**5.6**), makes the oxidation thermodynamically unfavourable. Each substrate was submitted to the C-H activation reaction for 24 hours using 5 equivalents of alkene. In each case, no C-H activation was observed. This supports our reaction pathway of alcohol oxidation and then C-H activation of the acetophenone.

**Figure 1 - Test Substrates**

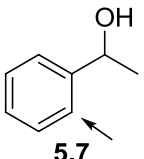
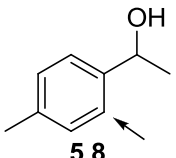
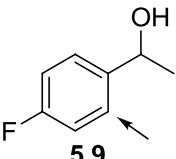
We were very pleased with the results obtained, as we had demonstrated not only that a tandem oxidation/C-H activation process was possible and successful, but furthermore, a third step could be added to the reaction sequence, providing three consecutive ruthenium-catalysed transformations in one pot. Whilst this is well known with other metals such as palladium,³⁴⁻³⁶ to the best of our knowledge this is the only ruthenium-catalysed example. In comparison, our example involves hydrogen transfer (oxidation), C-H activation and then transfer hydrogenation (reduction) requiring the catalyst to act in three different modes, rather than one mode for the same transformation three times.

5.3 Reaction Scope

**Scheme 4 - Sequential Oxidation/Alkylation/Reduction Conditions**

Having established an effective protocol for tandem oxidation/C-H activation followed by carbonyl reduction, a range of secondary benzylic alcohols was screened (Tables 2, 3 & 4).

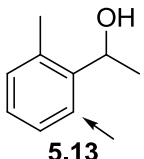
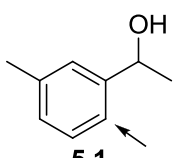
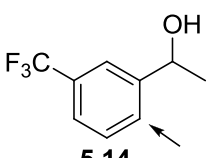
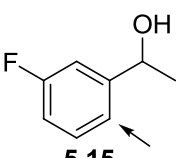
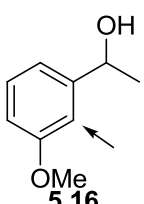
By tuning the number of equivalents of alkene and the reaction time it was possible to obtain a good ratio of mono-alkylated ketone with 1-phenethyl alcohol (**5.7**) and other para substituted alcohols. Furthermore, on addition of formic acid, only the mono-alkylated product was reduced to the alcohol, allowing easy separation and purification of the alcohols by silica column chromatography.

Entry ^a	Alcohol ^b	Time (h) ^c	Equivalents of Alkene	Isolated Yield (%)	Product
1		3	2.7	76	5.10
2		3	2.1	56	5.11
3		3.5	2.7	62	5.12

^a Conditions: Alcohol (1 mmol), 3,3-dimethylbut-1-ene, Ru(PPh₃)₃(CO)(H)₂ (5 mol%), toluene (1 mL), 135 °C, then formic acid (0.19 mL, 5 mmol), 135 °C, 3 h; ^b Arrow indicates position of substitution; ^c Time indicates the time for tandem oxidation/C-H activation.

Table 2 - Alkylated Alcohol Results

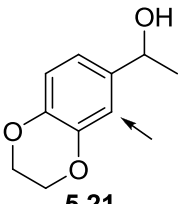
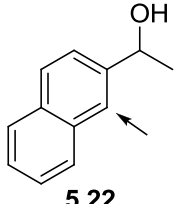
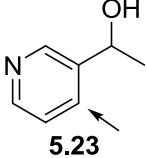
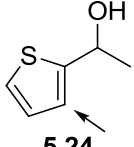
The results from Table 2 show that the reaction of 1-phenylethanol (**5.7**) gave good selectivity to the mono-alkylated product (Entry 1, Table 2). Despite the low equivalents of alkene, a large amount of disubstituted product was obtained when 1-*p*-tolylethanol was used as a substrate and thus resulted in a lower isolated yield. In comparison, no mono-substituted product could be isolated from the reaction of the para methoxy equivalent (Entry 7, Table 5), suggesting that the rate of the second alkylation is significantly faster than that of the first. The use of 1-*o*-tolylethanol (**5.13**) (Entry 1, Table 3) led to complete conversion of the alcohol; however, the reduction of the alkylated ketone to the product (**5.17**) was low yielding. This is probably due to the steric crowding around the carbonyl.

Entry ^a	Alcohol ^b	Time (h) ^c	Equivalents of Alkene	Isolated Yield (%)	Product
1	 5.13	3	2.3	41	5.17
2	 5.1	3	2.3	72	5.3
3	 5.14	3	2.3	87	5.18
4	 5.15	3	2.3	62	5.19
5	 5.16	4	2.3	70 ^d (79:21)	5.20

^a Conditions: Alcohol (1 mmol), 3,3-dimethylbut-1-ene, Ru(PPh₃)₃(CO)(H)₂ (5 mol%), toluene (1 mL), 135 °C, then formic acid (0.19 mL, 5 mmol), 135 °C, 3 h; ^b Arrow indicates position of substitution; ^c Time indicates the time for tandem oxidation/C-H activation; ^d Mixture of regioisomers, major isomer shown.

Table 3 - Meta-Substituted Alkylated Alcohol Results

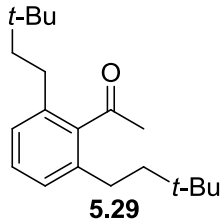
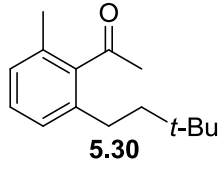
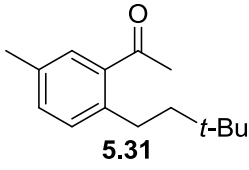
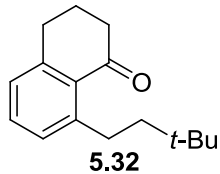
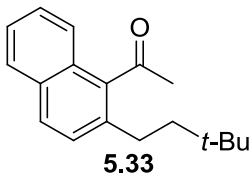
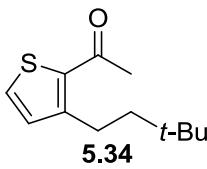
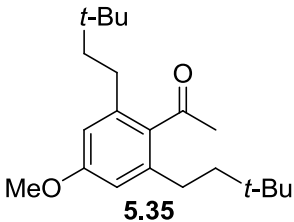
The use of meta substituted alcohols led to similar substitution patterns to those obtained by Murai with the alkylation of ketone.^{4,10} Both meta methyl (**5.1**) and meta trifluoromethyl (**5.14**) led to alkylation para to the substituent (Entries 2 & 3, Table 3). This suggests that the insertion of the ruthenium into the C-H bond is dictated by steric effects, however, when the meta fluoro alcohol (**5.15**) was used, the alkylation still occurred para to the substituent. In this case the difference in size of the fluorine and hydrogen atoms is negligible; indicating that the electronic nature of the aromatic ring also has a substantial effect.

Entry ^a	Alcohol ^b	Time (h) ^c	Equivalents of Alkene	Isolated Yield (%)	Product
1	 5.21	4	2.3	53	5.25
2	 5.22	3	2.3	89	5.26
3	 5.23	4	3	55	5.27
4	 5.24	24	3	55	5.28

^a Conditions: Alcohol (1 mmol), 3,3-dimethylbut-1-ene, Ru(PPh₃)₃(CO)(H)₂ (5 mol%), toluene (1 mL), 135 °C, then formic acid (0.19 mL, 5 mmol.), 135 °C, 3 h; ^b Arrow indicates position of substitution; ^c Time indicates the time for tandem oxidation/C-H activation.

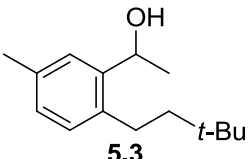
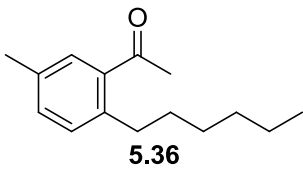
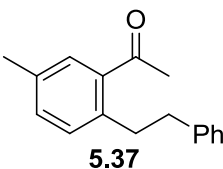
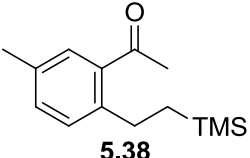
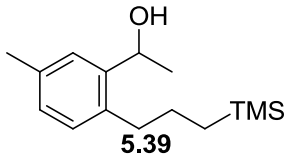
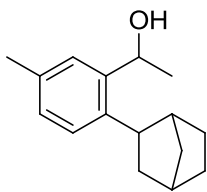
Table 4 - Other Alkylated Alcohols

The importance of electronic effects on the aryl ring was re-enforced by the result obtained with the meta methoxy alcohol (**5.16**) (Entry 5, Table 3) which gave a mixture of regioisomers (79:21). The major isomer had been alkylated at the most sterically hindered position, whilst the minor isomer was alkylated para to the methoxy group. This mixture confirms that both steric and electronic factors play an important role in determining which ortho C-H bond the ruthenium inserts into.^{4,10,14,37}

Entry ^a	Product	Time (h) ^b	Equivalents of Alkene	Isolated Yield (%)
1	 5.29	5	5	98
2	 5.30	3	2.3	97
3	 5.31	3	2.3	96
4	 5.32	6	2.3	81
5	 5.33	8	2.3	99
6	 5.34	24	3	76
7	 5.35	4	4	85

^a Conditions: Alcohol (1 mmol), 3,3-dimethylbut-1-ene, Ru(PPh₃)₃(CO)(H)₂ (5 mol%), toluene (1 mL), 135 °C; ^b Time indicates the time for tandem oxidation/C-H activation.

Table 5 - Tandem Oxidation/C-H Activation Products

Entry ^{a,b}	Product	Time (h) ^c	Equivalents of Alkene	Isolated Yield (%)
1	 5.3	3	2.3	72
2	 5.36	24	2.5	12 ^d
3	 5.37	24	4.5	67
4	 5.38	5	3	59 ^e (79:21)
5	 5.39	24	4.5	68
6	 5.40	3	2.3	84

^a Conditions: 1-*m*-Tolyethanol (1 mmol), alkene, Ru(PPh₃)₃(CO)(H)₂ (5 mol%), toluene (1 mL), 135 °C, then formic acid (0.19 mL, 5 mmol), 135 °C, 3 h; ^b Conditions: 1-*m*-Tolyethanol (1 mmol), alkene, Ru(PPh₃)₃(CO)(H)₂ (5 mol%), toluene (1 mL), 135 °C; ^c Time indicates time for tandem oxidation/C-H activation only; ^d Conversion determined by ¹H NMR; ^e The product was isolated as a mixture of mono- and di-alkylated product, the ratio is given in parentheses.

Table 6 - Alkene Scope

The alkylation of other alcohols using the optimised protocol was also successful (Table 4). Piperonyl alcohol (**5.21**) (Entry 1, Table 4) showed similar regioselectivity to that observed with the meta methoxy substrate (Entry 5, Table 3). Naphthalene derivatives also worked well (**5.22**) (Entry 2, Table 4), again alkylation occurred at the most hindered, but electronically activated position. It was also possible to use

heterocyclic alcohols (Entries 3 & 4, Table 4), although with slightly lower isolated yields.

Alkylated ketones from the tandem oxidation/alkylation could also be isolated (Table 5). Entries 1-3, Table 5 were isolated in good yield to illustrate that ketones could be isolated as ketones from the reaction mixture as well as alcohols. The use of both 1,2,3,4-tetrahydronaphthalen-1-ol and 1-(naphthalen-1-yl)ethanol gave good conversion through to the alkylated ketones (Entry 4 & 5, Table 5), but the reduction steps were poor. Interestingly, the use of a similar alcohol, 2,3-dihydro-1*H*-inden-1-ol resulted only in oxidation and no C-H activation. Murai also observed that no C-H activation occurred with this ketone, and proposed that the carbonyl was too far away from the ortho-aromatic protons to direct the insertion.⁵ The thienyl alcohol (Entry 6, Table 5) could be isolated as either the alcohol (Entry 4, Table 4) or the ketone, the latter in better yields. Finally, the 1-(4-methoxyphenyl)ethanol was isolated as the di-alkylated product (Entry 7, Table 5), as the mono-alkylated product was only observed as the minor product by ¹H NMR analysis.

A screen of alkenes was undertaken, with 1-hexene (Entry 2, Table 6) giving a similarly poor result to the one obtained by Murai.¹⁰ The alkylation with styrene (Entry 3, Table 6) required a longer reaction time to drive the reaction to completion. The use of a silylated alkene (Entries 4 & 5, Table 6) gave good results when an allyl group was used; however, when the vinyl silane was used, a mixture of mono- and di-alkylated product was isolated. This was attributed to the longer C-Si bond resulting in the steric bulk of the trimethylsilyl group being far enough away to allow di-substitution with the vinyl silane. It was also possible to use norbornene (Entry 6, Table 6) with the alkylation product being isolated as a mixture of diastereomers, in good yield.

5.4 CHAPTER SUMMARY

- A tandem oxidation/C-H activation of alcohols was developed.
- It was then possible to add a further reduction step, generating a one-pot, three step process to go from alcohol to alkylated alcohol.
- Various substituted alcohols, including heterocyclic examples, were isolated.
- Substrates that were difficult to reduce could be isolated as the alkylated ketones in good yields.

5.5 References

- [1] Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Nature* **1993**, *366*, 529-531.
- [2] Murai, S. *J. Syn. Org. Chem. Jpn.* **1994**, *52*, 992-1001.
- [3] Kakiuchi, F.; Yamamoto, Y.; Chatani, N.; Murai, S. *Chem. Lett.* **1995**, *8*, 681-682.
- [4] Sonoda, M.; Kakiuchi, F.; Chatani, N.; Murai, S. *J. Organomet. Chem.* **1995**, *504*, 151-152.
- [5] Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N.; Murai, S. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 62-83.
- [6] Kakiuchi, F.; Yamauchi, M.; Chatani, N.; Murai, S. *Chem. Lett.* **1996**, *2*, 111-112.
- [7] Sonoda, M.; Kakiuchi, F.; Kamatani, A.; Chatani, N.; Murai, S. *Chem. Lett.* **1996**, *2*, 109-110.
- [8] Fujii, N.; Kakiuchi, F.; Chatani, N.; Murai, S. *Chem. Lett.* **1996**, *11*, 939-940.
- [9] Murai, S.; Chatani, N.; Kakiuchi, F. *Pure Appl. Chem.* **1997**, *69*, 589-594.
- [10] Sonoda, M.; Kakiuchi, F.; Chatani, N.; Murai, S. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 3117-3128.
- [11] Kakiuchi, F.; Murai, S. *Acc. Chem. Res.* **2002**, *35*, 826-834.
- [12] Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077-1101.
- [13] Kakiuchi, F.; Kochi, T. *Synthesis* **2008**, *19*, 3013-3039.
- [14] Kakiuchi, F.; Kochi, T. Mizushima, E.; Murai, S. *J. Am. Chem. Soc.* **2010**, *132*, 17741-17750.
- [15] Bartoszewicz, A.; Martín-Matute, B. *Org. Lett.* **2009**, *11*, 1749-1752.
- [16] Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97-102.
- [17] Maytum, H. C.; Tavassoli, B.; Williams, J. M. J. *Org. Lett.* **2007**, *9*, 4387-4389.

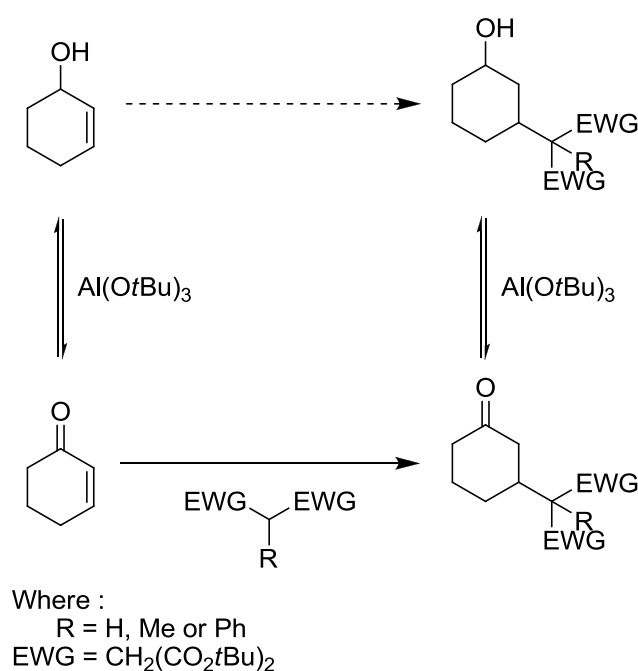
- [18] Maytum, H. C.; Francos, J.; Whatrup, D.; Williams, J. M. J. *Chem. Asian J.* **2010**, *5*, 538-542.
- [19] Czaun, M.; Goeppert, A.; May, R.; Haiges, R.; Prakash, G. K.; Olah, G. A. *ChemSusChem*, **2011**, *4*, 1241-1248.
- [20] Rigsby, M. A.; Zhou, W.-P.; Lewera, A.; Duong, H. T.; Bagus, P. S.; Jaegermann, W.; Hunger, R.; Wieckowski, A. *J. Phys. Chem. C*, **2008**, *112*, 15595-15601.
- [21] Avery, N. R.; Toby, B. H.; Anton, A. b.; Weinberg, W. H. *Surf. Sci. Lett.* **1982**, *122*, L574-L578.
- [22] Fujita, K.; Furukawa, S.; Yamaguchi, R. *J. Organomet. Chem.* **2002**, *649*, 289-292.
- [23] Suzuki, T.; Morita, K.; Matsuo, Y.; Hiroi, K. *Tetrahedron Lett.* **2003**, *44*, 2003-2006.
- [24] Fujita, K.; Yamaguchi, R. *Synlett* **2005**, *4*, 560-571.
- [25] Fujita, K.; Takahashi, Y.; Owaki, M.; Yamamoto, K.; Yamaguchi, R. *Org. Lett.* **2004**, *6*, 2785-2788.
- [26] Hanasaka, F.; Fujita, K.; Yamaguchi, R. *Organometallics* **2004**, *23*, 1490-1492.
- [27] Suzuki, T.; Matsuo, T.; Watanabe, K.; Katoh, T. *Synlett* **2005**, *9*, 1453-1455.
- [28] Hanasaka, F.; Fujita, K.; Yamaguchi, R. *Organometallics* **2005**, *24*, 3422-3433.
- [29] Izumi, A.; Obora, Y.; Sakaguchi, S.; Ishii, Y. *Tetrahedron Lett.* **2006**, *47*, 9199-9201.
- [30] Hanasaka, F.; Fujita, K.; Yamaguchi, R. *Organometallics* **2006**, *25*, 4643-4647.
- [31] Uematsu, N.; Fujii, A.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 4916-4917.
- [32] Vedejs, E.; Trapencieris, P.; Suna, E. *J. Org. Chem.* **1999**, *64*, 6724-6729.

- [33] Zhang, J.; Blaczecka, P. G.; Bruendl, M. M.; Huang, Y. *J. Org. Chem.* **2009**, *74*, 1411-1414.
- [34] Trost, B. M.; Shi, Y. *J. Am. Chem. Soc.* **1991**, *113*, 701-703.
- [35] Sugihara, T.; Copéret, C.; Owczarczyk, Z.; Harring, L. S.; Negishi, E. *J. Am. Chem. Soc.* **1994**, *116*, 7923-7924.
- [36] Abelman, M. M.; Overman, L. E. *J. Am. Chem. Soc.* **1988**, *110*, 2328-2329.
- [37] Hiraki, K.; Ishimoto, T.; Kawano, H. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 2099-2108.

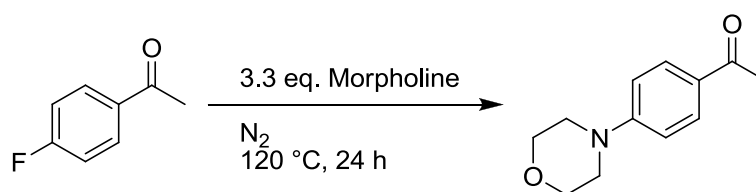
6 RESULTS AND DISCUSSION V

6.1 Background

The previous chapter demonstrated how hydrogen transfer methodology could be used to modify alcohols at positions remote to the hydroxy group by utilising C-H activation. Having succeeded in activating the ortho position of benzylic alcohols,¹ the potential to apply the idea of remote electronic activation to other functionalities was followed. Previous work from the Williams group has demonstrated that allylic alcohols can be activated towards nucleophilic additions of malonates² and stabilised nucleophiles²⁻³ via a borrowing hydrogen approach (Scheme 1).

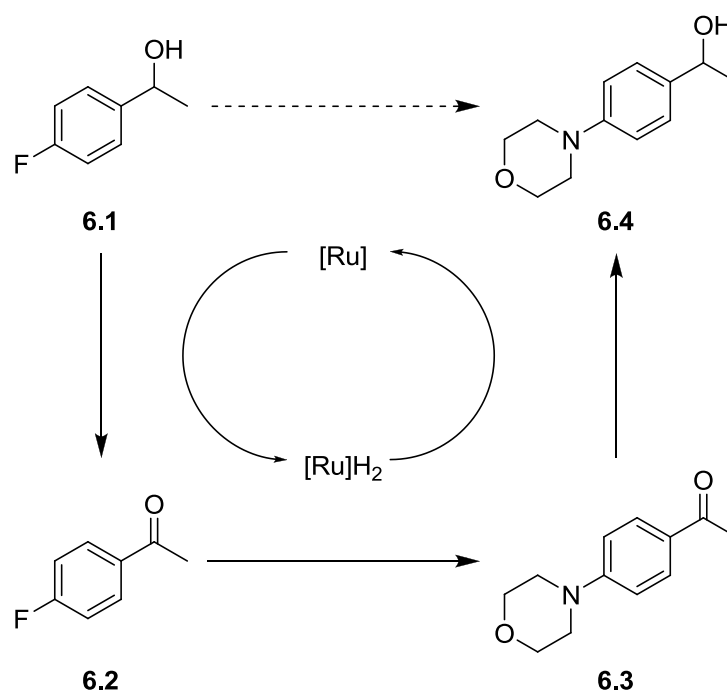


Scheme 1 - Remote Electronic Activation of Allylic Alcohols



Scheme 2 - Nucleophilic Substitution of Fluoroacetophenone

The nucleophilic aromatic substitution of activated fluorides in acetophenones is well reported (Scheme 2).⁴⁻⁶

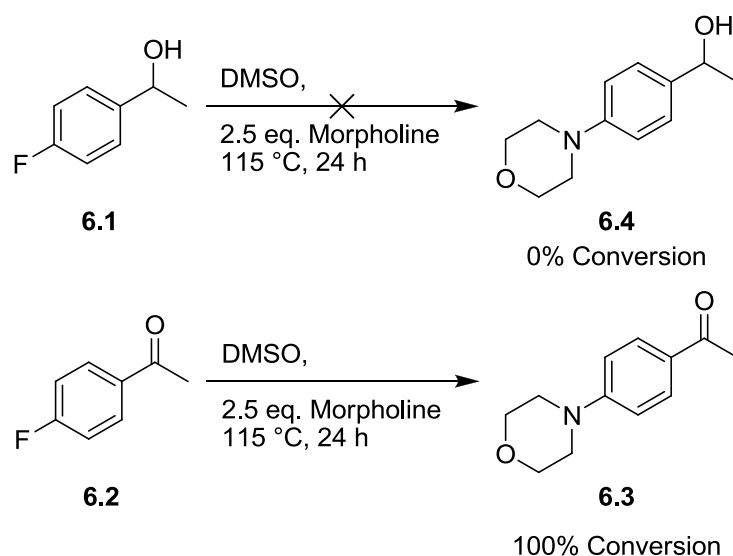


Scheme 3 - Proposed Application of the Borrowing Hydrogen Methodology to Activate Fluorine to Nucleophilic Aromatic Substitution

Modifying this reaction so that alcohols could be used (Scheme 3), *via* a borrowing hydrogen mechanism, would provide a new approach to borrowing hydrogen. This would demonstrate that borrowing hydrogen reactions can be performed that do not occur at the carbonyl centre, whilst adding a further example to the area of remote electronic activation.

6.2 Initial Studies

Initial work focused on applying a borrowing hydrogen methodology to the substitution of 4-fluoro-substituted secondary alcohols (Scheme 3). In order for this process to be viable, the conversion of the alcohol (**6.1**) into the product alcohol (**6.4**) must not happen without the need for the catalysis. Accordingly, this reaction was the first tested (Scheme 4). As expected, this reaction did not proceed and no product or other by-products were observed in the analysis of the 1H NMR, only return of the starting materials.



Scheme 4 - Test for Aromatic Substitution

Having established that the alcohol would not undergo the reaction, the 4-fluoro ketone (**6.2**) was also tested under the same reaction conditions, to ensure the desired reaction would proceed as reported in the literature. As expected the reaction went to 100% conversion by analysis of the ^1H NMR (Scheme 4). Interestingly, attempts to use 4-bromo or 4-chloro acetophenone under these conditions were unsuccessful.

A review of the literature revealed that DMF and DMSO were the two solvents of choice for the substitution reaction, a screen of other solvents confirmed that indeed the reaction did not occur or did so with a lower conversion. Contrary to literature reports, a better conversion was observed in DMSO compared with DMF, and so DMSO was chosen as the reaction solvent. A variety of bases have been reported in the literature for the substitution reaction and a screen of inorganic and organic bases was conducted to determine which would be most suitable (Table 1).

Analysis of the results showed that several of the bases led to by-product formation, clearly visible by a new set of doublets in the aromatic region of the ^1H NMR spectra, which were not associated with the desired product. These bases were therefore discounted and further work concentrated on the bases that gave the highest conversion without by-product formation. The best result was obtained with triethylamine (Entry 11, Table 1) which gave 34% conversion after 3 hours. A linear extrapolation of this result, would give full conversion after 9 hours, however in practice the reaction had only reached 71% conversion after 12 hours (Table 1, Entry 12), suggesting a tail off in the rate of reaction.

Entry ^a	Base	Conversion (%) ^b
1	No Base ^c	33
2	NaOH	N. D. ^d
3	KOH	N. D. ^d
4	NaHCO ₃	0
5	KHCO ₃	0
6	Na ₂ CO ₃	21
7	K ₂ CO ₃	22
8	Cs ₂ CO ₃	N. D. ^d
9	KOt-Bu	N. D. ^d
10	K ₃ PO ₄	23
11	Et ₃ N	34
12	Et ₃ N ^e	71

^aConditions: 4-Fluoroacetophenone (1 mmol), morpholine (1.1 mmol), base (1.2 mmol), DMSO (1 mL), 115 °C, 3 h;

^bConversion determined by ¹H NMR; ^c2.2 mmol of morpholine used in this case; ^dBy-products were visible by

¹H NMR so the conversion was not determined; ^e12 h.

Table 1 - Base Screen

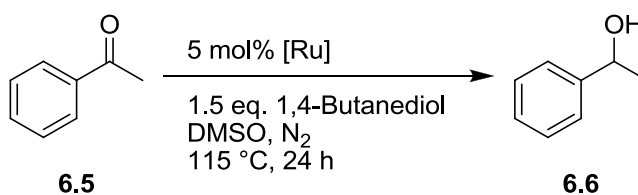
Entry ^a	Base	Equivalents of Base ^b	Conversion (%) ^c
1	Et ₃ N	1.2	77
2	DABCO	1.2	65
3	Hünig's Base	1.2	66
4	Tripropylamine	1.2	63
5	N-Ethyl morpholine	1.2	57
6	K ₂ CO ₃	1.2	38
7	Et ₃ N	1.5	80
8	Et ₃ N	2.0	65
9	No Base ^d	-	100

^aConditions: 4-Fluoroacetophenone (1 mmol), morpholine (1.1 mmol), base, DMSO (1 mL), 115 °C, 24 h; ^bRelative to the amount of ketone; ^cConversion determined by ¹H NMR; ^d2.2 mmol of morpholine used.

Table 2 - Further Base Screen

From all the results, triethylamine had consistently been the superior base; however, the reaction had not gone to completion which is necessary to obtain a good yield of the final amino alcohol. The number of equivalents of base was examined, to see if

the reaction could be driven to completion. Initial results looked good, with an increase to 1.5 equivalents of triethylamine giving a conversion of 80% after 24 hours (Table 2, Entry 7), however, a further increase to 2 equivalents led to a drop in conversion to 65% (Table 2, Entry 8). A return to the use of an excess of morpholine (Table 2, Entry 9) gave full conversion after 24 hours (Table 2, Entry 9). While this provides a solution, driving the substitution to 100% conversion, it is not ideal as an excess of amine is required. It is also not possible to use a sacrificial primary or secondary amine as this would lead to competitive substitution, leading to a mixture of products.



Scheme 5 - Hydrogen Transfer Test in DMSO

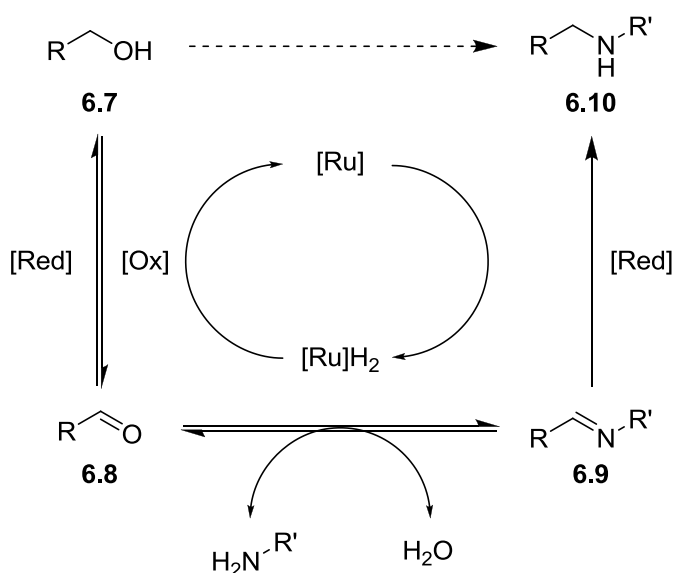
Having established that an excess of secondary amine gave the best results rather than the addition of a base it was necessary to focus on the catalyst options. A range of catalysts was screened in a simple irreversible hydrogen transfer reaction (Scheme 5) previously reported by the Williams group⁷ to determine which catalysts were active in DMSO (Table 3).

The results showed that only half the catalysts screened were active for hydrogen transfer in DMSO. While some catalyst deactivation was expected, the large number of catalysts that showed no activity was surprising. However, three commercially available catalysts did show activity (Table 3, Entries 4-6). Of these, $\text{Ru}(\text{PPh}_3)_3(\text{CO})(\text{H})_2$ (Table 3, Entry 5) was the most active, whilst the hydrochloride variant $\text{Ru}(\text{PPh}_3)_3(\text{CO})(\text{H})(\text{Cl})$ (Table 3, Entry 6) showed significantly less activity. Accordingly the dihydride catalyst was chosen for further work.

Entry ^a	Catalyst	Conversion (%) ^b
1	[Ru(<i>p</i> -cymene)Cl ₂] ₂	0
2	RuCl ₂ (PPh ₃) ₃	0
3	Ru ₃ (CO) ₁₂ ^c	0
4	Shvo's Catalyst	23
5	Ru(PPh ₃) ₃ (CO)(H) ₂	93
6	Ru(PPh ₃) ₃ (CO)(H)(Cl)	28

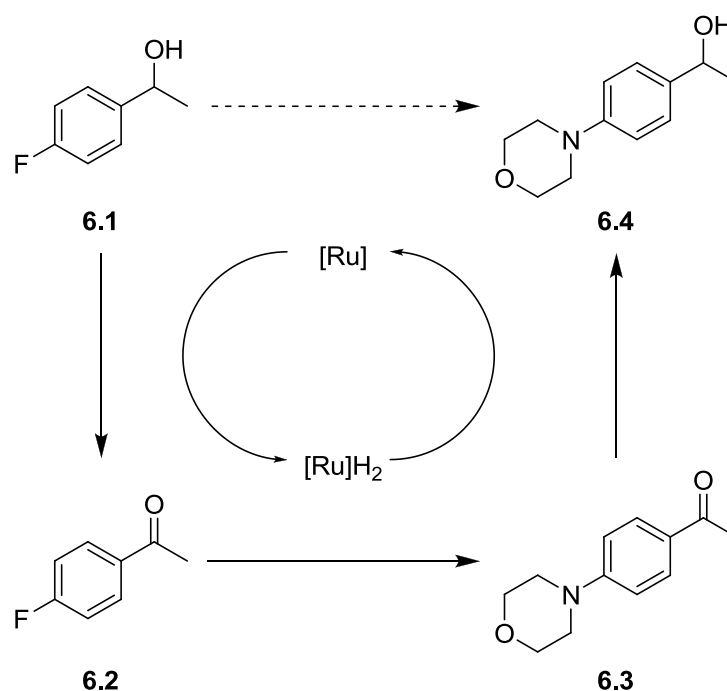
^aConditions: Acetophenone (1 mmol), 1,4-Butanediol (1.5 mmol), [Ru] (5 mol%), DMSO (1 mL), 115 °C, 24 h; ^bDetermined by ¹H NMR; ^c2 mol% catalyst used, meaning 6 mol% [Ru].

Table 3 - Catalyst Screen



Scheme 6 - Amine Formation Using Borrowing Hydrogen

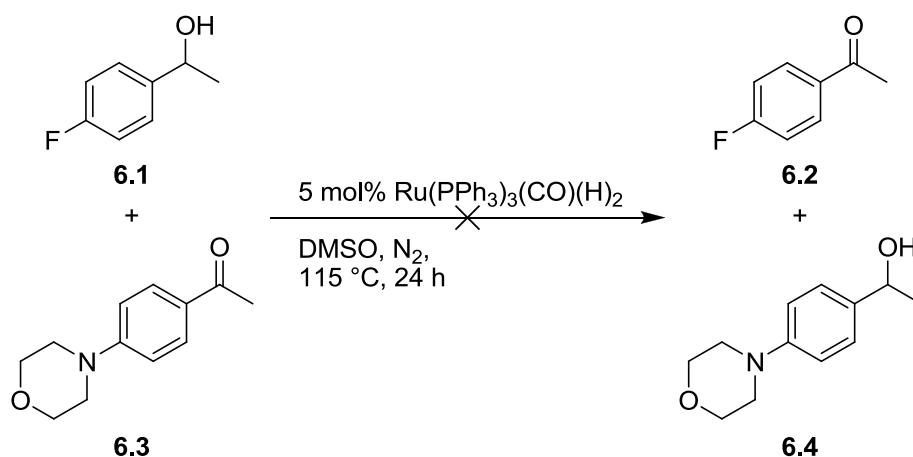
In a borrowing hydrogen reaction, one or two of the reaction steps can be reversible or at equilibrium, provided one is irreversible to drive the reaction to completion. For example, in amine formation (Scheme 6), the oxidation of the alcohol (**6.7**) to the aldehyde (**6.8**) is reversible, as is the formation of the imine (**6.9**) from the aldehyde (**6.8**). However, due to the conditions used, the reduction of the imine (**6.9**) to the secondary amine (**6.10**) is not reversible which drives the formation of the amine to completion.



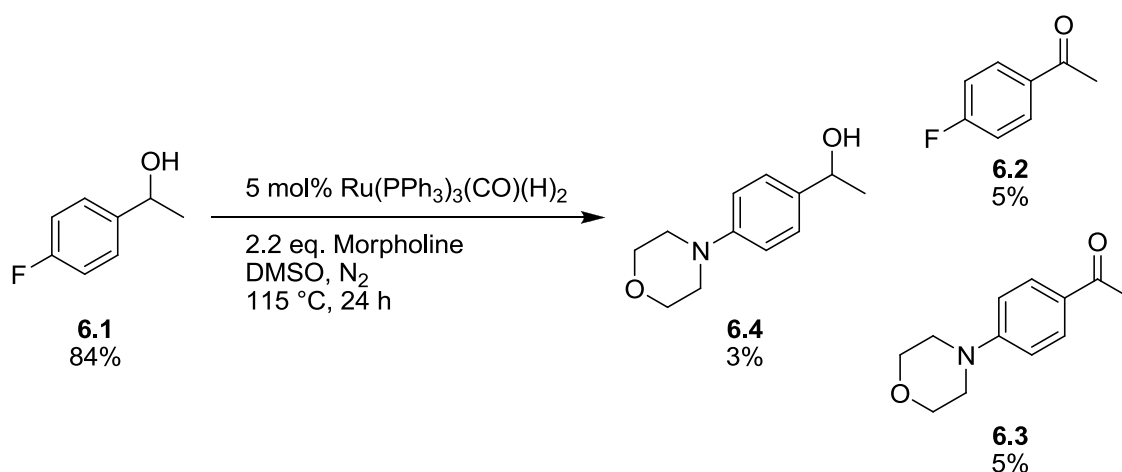
Scheme 7 - Proposed Application of the Borrowing Hydrogen Methodology to Activate Fluorine to Nucleophilic Aromatic Substitution

In order for the proposed reaction to proceed (Scheme 7), there must be a transfer of hydrogen atoms between the starting alcohol (**6.1**) and the product ketone (**6.3**). Without this, the reaction may stall as the active sites on the catalyst would be blocked by the hydrogen atoms removed in the initial oxidation, or give an undesired result by eliminating molecular hydrogen⁸⁻¹¹ resulting in formation of the aminated ketone (**6.3**) only and not the desired amino alcohol (**6.4**).

With this in mind, it was decided to test this key crossover reaction to ensure that the reaction would indeed proceed as desired (Scheme 8). Analysis of the reaction by ¹H NMR showed no indication of either **6.2** or **6.4** meaning that the crossover reaction necessary for the borrowing hydrogen strategy to work was not occurring. Nevertheless, a test of the actual reaction was run (Scheme 9).



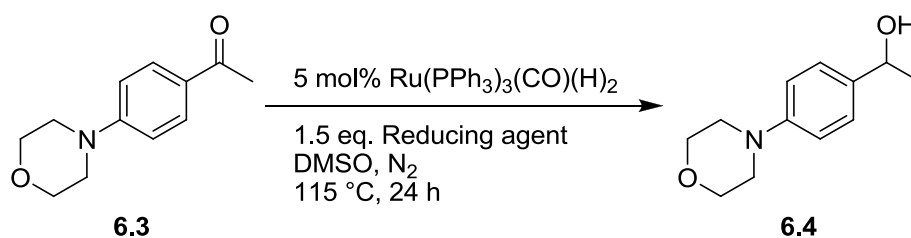
Scheme 8 - Crossover Reaction



Scheme 9 - Full Test of Borrowing Hydrogen Reaction

Analysis of the reaction mixture by ^1H NMR showed that the reaction had indeed proceeded to yield some of the desired product (6.4), although only in small amounts (3% conversion). An overall assessment of the reaction demonstrated that while the desired pathway was operating, the majority of the reaction mixture was still starting material (6.1). This agrees with the result obtained in the crossover reaction (Scheme 8) and strongly suggests that the equilibrium lies in a disfavoured position.

At this point, it was decided to approach the problem in a similar manner to that described in chapter 6; have a tandem oxidation and substitution and then add a reducing agent. As the reduction of the aminoketone (6.3) was known to be difficult, this was screened first (Scheme 10, Table 4).

Scheme 10 - Reduction Screen of Aminoketone **6.3**

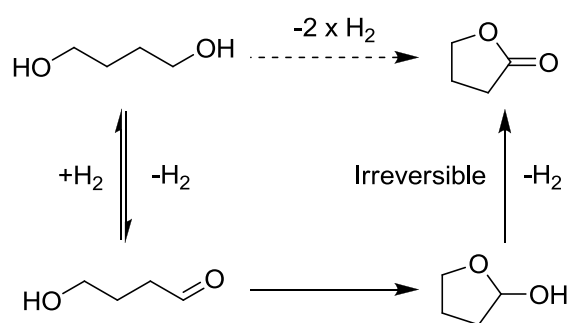
Entry ^a	Reducing Agent	Conversion (%) ^b
1	Formic Acid	45
2	1,4-Butanediol	63
3	Isopropanol	25 ^c
4	6.1	0

^aConditions: **6.3** (1 mmol), reducing agent (1.5 mmol), Ru(PPh₃)₃(CO)(H)₂ (5 mol%), DMSO (1 mL), 115 °C, 24 h;

^bConversion determined by ¹H NMR; ^c 13 mmol of isopropanol (1 mL) were used.

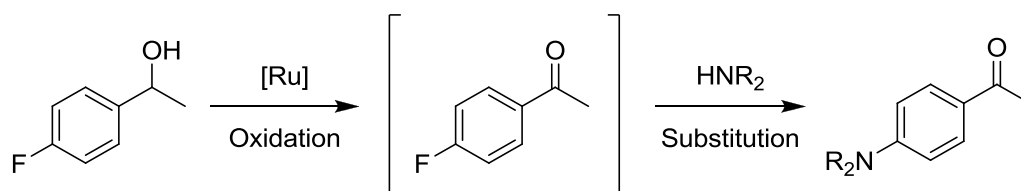
Table 4 - Reduction Screen

A short screen of reducing agents quickly demonstrated that 1,4-butanediol was a good source of hydrogen to reduce the aminoketone (Entry 2, Table 4). When compared to isopropanol (Entry 3, Table 4), it can be seen why the 1,4-butanediol is a useful source of hydrogen as the lactone generated when 1,4-butanediol is oxidised makes the reaction irreversible (Scheme 11).⁷ It should also be noted that again **6.1** (Entry 4, Table 4) was unsuccessful as a reducing agent for the aminoketone (**6.3**).



Scheme 11 - Irreversible Hydrogen Generation from 1,4-Butanediol

Having established that the reduction could be achieved, and with further modifications to improve the yield, attention was turned to the tandem oxidation/substitution reaction (Scheme 12).



Scheme 12 - Tandem Oxidation/Substitution Process

Based on the results obtained earlier, it was then necessary to screen a series of oxidants for the reaction. Alkenes were chosen over the use of other organic hydrogen acceptors such as ketones¹²⁻¹⁵ or crotonitrile¹⁶⁻¹⁸ due to their relatively inert nature with respect to the other reaction components. The secondary amine could react with a ketone to form an enamine or iminium species, while amines have been shown to react with crotonitrile itself irreversibly. A screen of the readily available alkenes was conducted and the results are shown below (Table 5).

Entry ^a	Oxidant	Conversion (%) ^b
1		24
2		6
3		22
4		34
5		28

^aConditions: 1-(4-Fluorophenyl)ethanol (1 mmol), morpholine (2.2 mmol), oxidant (1.5 mmol), Ru(PPh₃)₃(CO)(H)₂ (5 mol%), DMSO (1 mL), 115 °C, 24 h; ^bDetermined by analysis of the ¹H NMR spectra.

Table 5 - Oxidant Screen

Terminal alkenes tend to give better results; the only example of a non-terminal alkene was cyclohexene (Table 5, Entry 2) which only resulted in 6% conversion. The two best alkenes were 3,3-dimethyl-1-butene (Entry 5, Table 5) and 1-octene (Entry 4, Table 5). Of these, 1-octene was chosen due to its higher boiling point,

despite the slightly lower atom economy. A series of ligands was then studied to see if the extent of the oxidation could be improved (Table 6).

Entry ^a	Ligand	Conversion (%) ^b
1	dppm	48
2	dppe	47
3	dppp	34
4	dppb	24
5	dpppent	15
6	Triphos	10
7	Xantphos	41
8	DPEphos	17
9	(+/-)-BINAP	33
10	dppbe	41
11	1,2-Bis(dicyclohexylphosphino)ethane	60
12	<i>cis</i> -1,2-Bis(diphenylphosphino)ethylene	30

^aConditions: 1-(4-Fluorophenyl)ethanol (1 mmol), 1-octene (1.5 mmol), Ru(PPh₃)₃(CO)(H)₂ (5 mol%), ligand (5 mol%), DMSO (1 mL), 115 °C, 24 h;

^bDetermined by analysis of the ¹H NMR spectra.

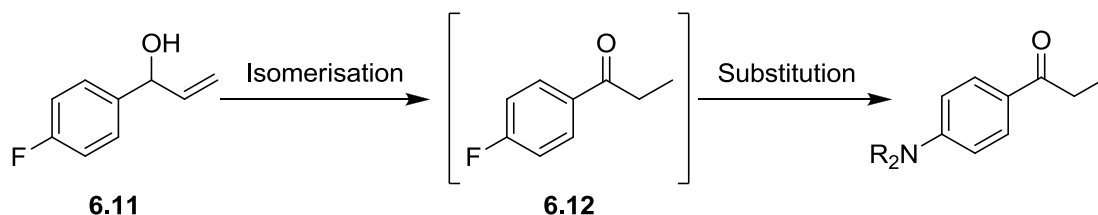
Table 6 - Ligand Screen

Analysis of the ligand screen revealed 4 ligands with similar activity; dppm, dppe, Xantphos and dppbe all giving 40-50% conversion (Entries 1, 2, 7 & 10, Table 6). However, the best ligand was 1,2-bis(dicyclohexylphosphino)ethane (Entry 11, Table 6). Due to the increased conversion afforded by this ligand (~10-15% better than any other ligand) it was taken forward for further optimisation.

In order to increase the conversion, an increase in reaction temperature was necessary. However, on increasing the reaction temperature the reaction conversion decreased, indicating that 115 °C was optimal, although this only resulted in a 60% conversion after 24 hours. We did not want to increase the reaction time to 48 hours and so, work on the tandem oxidation/substitution followed by reduction was halted.

The idea of combining the aromatic nucleophilic substitution with another step was very appealing, and with the amount of work already done on the application, it was disappointing that the tandem oxidation/substitution could not be implemented. The aromatic substitution reaction requires an aromatic ketone as the substrate, we chose to generate this *via* an oxidation of the alcohol, however, a redox neutral approach

would work with a vinylic alcohol (**6.11**) that could be isomerised into the ketone (**6.12**) (Scheme 13).



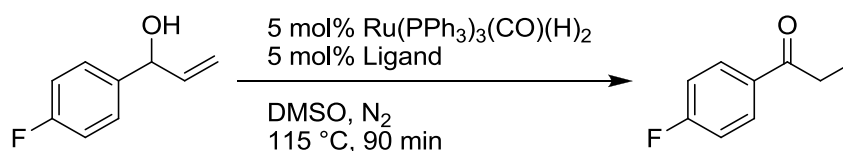
Scheme 13 - Redox Neutral Isomerisation

Transition metal catalysed isomerisations of allylic alcohols to carbonyl compounds have well reported.¹⁹⁻²⁰ The use of ruthenium to isomerise vinylic alcohols to ketones is also well reported²¹ and applications of this chemistry in tandem processes have also been reported.²²⁻²⁵ So this appeared to be an approach worth evaluating.

Based on the work described above, DMSO was still the solvent of choice and similarly Ru(PPh)₃(CO)(H)₂ was chosen as catalyst. With the catalyst and solvent established a ligand screen was run to determine which ligands might be suitable (Scheme 14 & Table 7).

Analysis of the ligand screen showed that most of the ligands used gave little improvement in conversion over the use of no ligand at all (Entry 1, Table 7). The two ligands that stood out were DPEphos (Entry 9, Table 7) and 1,4-bis(dicyclohexylphosphino)butane (Entry 13, Table 7). A cost analysis of these two ligands shows that DPEphos is the cheaper at £2.10 per mmol while 1,4-bis(dicyclohexylphosphino)butane is at least 10 times more expensive at £29.10 per mmol. We therefore chose to carry out further optimisation of the reaction with DPEphos as the ligand of choice. Extension of the reaction time from 90 minutes to 3 hours (Entry 15, Table 7) resulted in 71% conversion, suggesting either an activation period or tailing off of reactivity. However, a further increase in reaction time to 5 hours led to 81% conversion by ¹H NMR analysis (Entry 16, Table 7).

A test of the tandem isomerisation and addition did not give the same conversion after 5 hours, suggesting that the effectiveness of the catalyst was reduced by the addition of the amine. However, when left for 24 hours the reaction proceeded to complete conversion. It was also possible to reduce the catalyst loading to 4 mol% without further reducing the conversion with a reaction time of 24 hours.



Scheme 14 - Isomerisation Ligand Screen

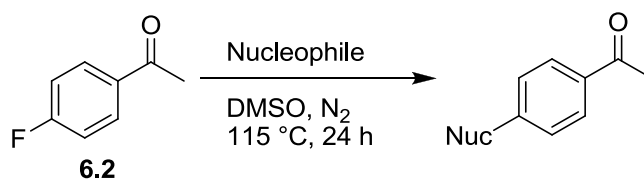
Entry ^a	Ligand	Conversion (%) ^b
1	No Ligand	13
2	dppm	16
3	dppe	19
4	dppp	35
5	dppb	20
6	dpppent	13
7	Triphos	15
8	Xantphos	27
9	DPEphos	50
10	(+/-)-BINAP	12
11	dppbe	16
12	1,2-Bis(dicyclohexylphosphino)ethane	27
13	1,4-Bis(dicyclohexylphosphino)butane	58
14	<i>cis</i> -1,2-Bis(diphenylphosphino)ethylene	17
15	DPEphos	71 ^c
16	DPEphos	81 ^d

^aConditions: 1-(4-Fluorophenyl)prop-2-en-1-ol (1 mmol), Ru(PPh₃)₃(CO)(H)₂ (5 mol%), ligand (5 mol%), DMSO (1 mL), 115 °C, 90 min; ^bConversion determined by ¹H NMR;

^cReaction run for 3 h; ^dReaction run for 5 h.

Table 7 - Isomerisation Ligand Screen

To this point, only morpholine had been used as a nucleophile, but to demonstrate the generality of the process, it was important to determine which other amines and nitrogen containing nucleophiles could be used (Scheme 15 & Table 8). As our model substrate (1-(4-fluorophenyl)prop-1-en-2-ol) was not commercially available, we chose to test the nucleophiles on 4-fluoroacetophenone (**6.2**) initially. Malonates, sulfonamides and amides were all found not to react.



Scheme 15 - Nucleophile Screen

Entry ^a	Nucleophile	Conversion (%) ^b
1	<p style="text-align: center;">6.13</p>	23
2	<p style="text-align: center;">6.14</p>	0
3	<p style="text-align: center;">6.15</p>	0
4	<p style="text-align: center;">6.16</p>	0
5	<p style="text-align: center;">6.17</p>	18 ^c
6	<p style="text-align: center;">6.17</p>	0 ^d
7		100

^a Conditions: 4-Fluoroacetophenone (1 mmol), amine (2.2 mmol), DMSO (1 mL), 115 °C, 24 h; ^b Conversion determined by ¹H NMR; ^c 1.1 mmol of pyrrole and 1.1 mmol of K₂CO₃ used instead of 2.2 mmol amine; ^d Conditions as per entry 5 but using DMF as the reaction solvent.

Table 8 - Nucleophile Screen

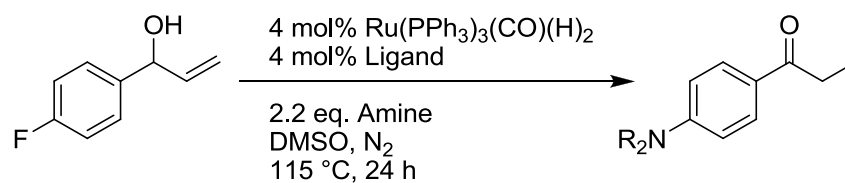
The results of the nucleophile screen were disappointing. The use of other acyclic secondary amines such as dipropylamine (**6.13**) (Entry 1, Table 8) and diisopropylamine (**6.14**) (Entry 2, Table 8) gave low or no conversion returning only starting materials. The use of primary amines such as *tert*-octylamine (**6.15**) (Entry 3,

Table 8) or aniline (**6.16**) (Entry 4, Table 8) gave no conversion either. Despite a report in the literature using pyrrole²⁶ (**6.17**), this also gave no conversion (Entry 5, Table 8) even under the reported conditions using DMF as a solvent (Entry 6, Table 8).

6.3 Reaction Scope

Having established that only secondary cyclic amines worked particularly well in the reaction, a screen of other substrates of this type was run (Table 9). Analysis of all the results showed the reaction to be working well with < 70% isolated yield in every case. 5, 6 and 7 membered rings were all tolerated well (Entries 1-3, Table 9) and the inclusion of heteroatoms in the 4-position on six membered rings also caused no difficulties (Entries 4 & 5, Table 9).

The effect of substitution on the double bond was then examined (Table 10). Inclusion of a methyl group on the most substituted carbon (**6.28**) led to a lower isolated yield (Entry 2, Table 10). A similar result was obtained when the substrate possessed two methyl groups on the least substituted carbon (**6.29**) (Entry 3, Table 10). Furthermore, inclusion of a methyl group in the most substituted and least substituted position (**6.30**) (Entry 4, Table 10) gave no product at all and instead led to isomerisation to give the *cis*-isomer. Although in all cases a higher catalyst loading (5 mol%) and longer reaction time (48 hours) was required to drive the reaction further. This indicates that steric bulk around the double bond has a large influence on the rate of reaction. The inclusion of a phenyl group (**6.31**) (Entry 5, Table 10) also has a dramatic effect on the course of the reaction (37% isolated yield), indicating that electronic as well as steric effects dictate the rate of isomerisation. Finally, the use of an allyl alcohol (**6.32**) (Entry 5, Table 10) returned a good yield demonstrating that the reaction is not only limited to vinyl alcohols, but other longer chain alcohols can also be transformed under the same conditions.

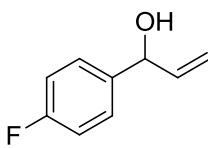
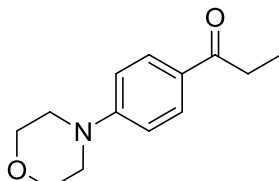
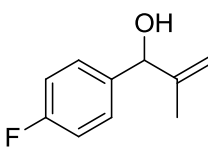
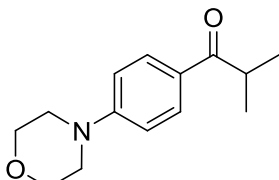
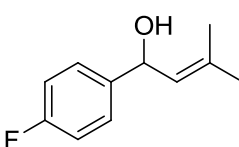
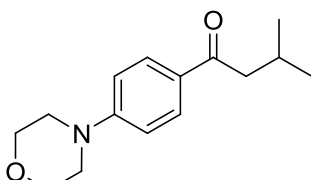
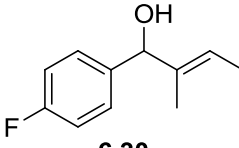
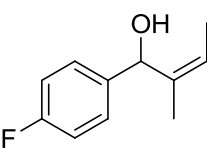
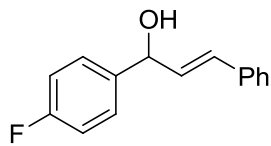
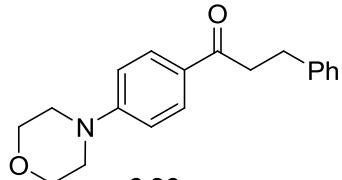
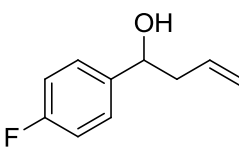
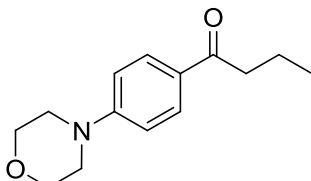


Scheme 16 - Optimised Reaction Conditions

Entry ^a	Amine	Isolated Yield (%)	Product
1	 6.18	77	 6.23
2	 6.19	87	 6.24
3	 6.20	81	 6.25
4	 6.21	86	 6.26
5	 6.22	71	 6.27

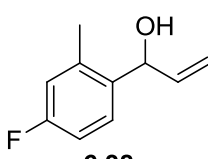
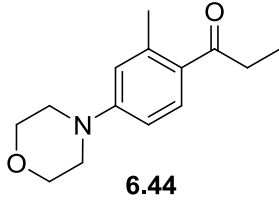
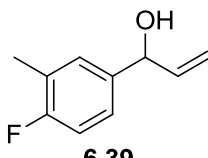
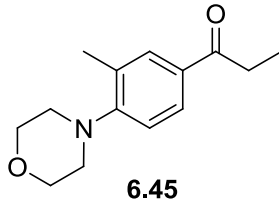
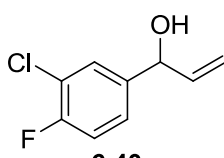
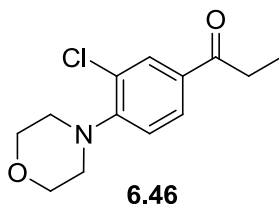
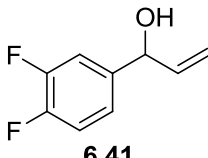
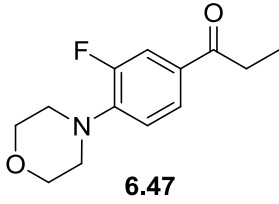
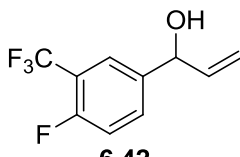
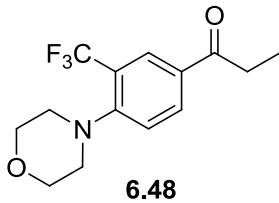
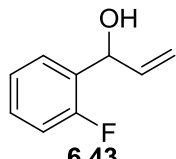
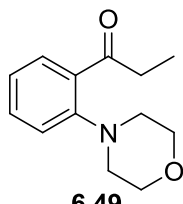
^aConditions: 1-(4-Fluorophenyl)prop-2-en-1-ol (3 mmol), amine (2.2 mmol), $\text{Ru}(\text{PPh}_3)_3(\text{CO})(\text{H})_2$ (4 mol%), DPEphos (4 mol%), DMSO (3 mL), 115 °C, 24 h.

Table 9 - Cyclic Amine Screen

Entry ^a	Alcohol	Isolated Yield (%)	Product
1	 6.11	86	 6.26
2	 6.28	52 ^{b,c}	 6.33
3	 6.29	57 ^{b,c}	 6.34
4	 6.30	0 ^{b,c}	 6.35
5	 6.31	37 ^{b,c}	 6.36
6	 6.32	85	 6.37

^aConditions: Alcohol (3 mmol), morpholine (2.2 mmol), Ru(PPh₃)₃(CO)(H)₂ (4 mol%), DPEphos (5 mol%), DMSO (3 mL), 115 °C, 24 h; ^b5 mol% catalyst; ^c48 h.

Table 10 - Double Bond Substitution

Entry ^a	Alcohol	Isolated Yield (%)	Product
1	 6.38	51	 6.44
2	 6.39	6 ^d (74) ^e	 6.45
3	 6.40	58	 6.46
4	 6.41	67	 6.47
5	 6.42	61	 6.48
6	 6.43	35 ^{b,c}	 6.49

^aConditions: Alcohol (3 mmol), morpholine (2.2 mmol), Ru(PPh₃)₃(CO)(H)₂ (4 mol%), DPEphos (4 mol%), DMSO (3 mL), 115 °C, 24 h; ^b5 mol% catalyst; ^c48 h; ^dConversion determined by ¹H NMR; ^eIsolated yield of ketone.

Table 11 - Ring Substitution

Substitution around the aromatic ring was examined, as this would be likely to affect the rate of aromatic substitution. The inclusion of a methyl group meta to the fluorine (**6.38**) (Entry 1, Table 11) did reduce the yield to 51%, however, inclusion of the methyl ortho to the fluorine (**6.39**) (Entry 2, Table 11) had a more dramatic effect

resulting in only 6% substitution. This could be the result of either steric or electronic effects, in this case it would seem reasonable that this is mainly due to the electron donating nature of the methyl group since substitution with both ortho chloro (**6.40**) (Entry 3, Table 11) and ortho trifluoromethyl (**6.42**) (Entry 5, Table 11) result in 58% and 61% yields. If this were due to steric effects, then the results of these other two reactions would also be expected to be lower, but not in this case. It was also possible to see selective substitution of the fluorine para to the ketone, as expected, when the 3,4-difluoro alcohol was used (**6.41**) (Entry 4, Table 11). The reaction also tolerated fluorine ortho to the ketone (**6.43**) (Entry 6, Table 11) although yields were lower.

It is worth noting that at no point during any of this work was a product from C-N bond formation observed *via* the borrowing hydrogen reaction of an amine and alcohol.

6.4 CHAPTER SUMMARY

- A borrowing hydrogen approach to aromatic substitution of ketones was explored.
- A tandem oxidation/substitution approach to aromatic substitution of ketones was also explored.
- A tandem isomerisation/substitution was explored and proved to be successful and was optimised.
- A wide range of substrates was evaluated illustrating the scope of the reaction, including substitution on the alkene, aromatic ring and choice of nucleophiles available.

6.5 References

- [1] Watson, A. J. A.; Maxwell, A. C.; Williams, J. M. J. *Org. Lett.* **2010**, *12*, 3856-3859.
- [2] Black, P. J.; Edwards, M. G.; Williams, J. M. J. *Tetrahedron*. **2005**, *61*, 1363-1374.
- [3] Black, P. J.; Harris, W.; Williams, J. M. J. *Angew. Chem. Int. Ed.* **2001**, *40*, 4475-4476.
- [4] Kotsuki, H.; Kobayashi, S.; Matsumoto, K. Suenaga, H.; Nishizawa, H. *Synthesis* **1990**, *12*, 1147-1148.
- [5] Wei, T. U. S. Patent 0171581 A1, **2003**.
- [6] Rhodes, D. I.; Macfarlane, K.; Jones, E. D.; Issa, W.; Deadman, J. J.; Choi, N. U. S. Patent 124546 A1, **2007**.
- [7] Maytum, H. C.; Tavassoli, B.; Williams, J. M. J. *Org. Lett.* **2007**, *9*, 4387-4389.
- [8] Choi, J. H.; Kim, N.; Shin, Y. J.; Park, J. H.; Park, J. *Tetrahedron Lett.* **2004**, *45*, 4607.
- [9] Junge, H.; Beller, M. *Tetrahedron Lett.* **2005**, *46*, 1031-1034.
- [10] Adair, G. R. A.; Williams, J. M. J. *Tetrahedron Lett.* **2005**, *46*, 8233-8235.
- [11] Kim, W.-H.; Park, I. S.; Park, J. *Org. Lett.* **2006**, *8*, 2543-2545.
- [12] Fujita, K.; Furukawa, S.; Yamaguchi, R. *J. Organomet. Chem.* **2002**, *649*, 289-292.
- [13] Suzuki, T.; Morita, K.; Tsuchida, M.; Hiroi, K. *J. Org. Chem.* **2003**, *68*, 1601-1602.
- [14] Yamamoto, N.; Obora, Y.; Ishii, Y. *J. Org. Chem.* **2011**, *76*, 2937-2941.
- [15] Watson, A. J. A.; Maxwell, A. C.; Williams, J. M. J. *Org. Lett.* **2009**, *11*, 2667-2670.
- [16] Owston, N. A.; Parker, A. J.; Williams, J. M. J. *Chem. Commun.* **2008**, 624-625.

- [17] Hall, M. I.; Pridmore, S. J.; Williams, J. M. J. *Adv. Synth. Catal.* **2008**, 350, 1975-1978.
- [18] Owston, N. A.; Nixon, T. D.; Parker, A. J.; Whittlesey, M. K.; Williams, J. M. J. *Synthesis* **2009**, 9, 1578-1581.
- [19] Uma, R.; Crévisy, C.; Grée, R. *Chem. Rev.* **2003**, 103, 27-51.
- [20] van der Drift, R. C.; Bouwman, E.; Drent, E. *J. Organomet. Chem.* **2002**, 650, 1-24.
- [21] Cadierno, V.; Crochet, P.; Gimeno, J. *Synlett* **2008**, 8, 1105-1124.
- [22] Cadierno, V.; Francos, J.; Gimeno, J.; Nebra, N. *Chem. Commun.* **2007**, 2536-2538.
- [23] Maytum, H. C.; Francos, J.; Whatrup, D. J.; Williams, J. M. J. *Chem. Asian. J.* **2010**, 5, 538-542.
- [24] Bartoszewicz, A.; Martín-Matute, B. *Org. Lett.* **2009**, 11, 1749-1752.
- [25] Ahlsten, N.; Bartoszewicz, A.; Agrawal, S.; Martín-Matute, B. *Synthesis*, **2011**, 16, 2600-2608.
- [26] Mishra, N.; Arora, P.; Kumar, B.; Mishra, L. C.; Bhattacharya, A.; Awashti, S. K.; Bhasin, V. K. *Eur. J. Med. Chem.* **2008**, 43, 1530-1535.

7 EXPERIMENTAL DATA

7.1 General Experimental Methods

Reactions which required the use of anhydrous, inert atmosphere techniques were carried out under an atmosphere of nitrogen. In all cases, solvents were distilled or obtained by passing through anhydrous alumina columns using an Innovative Technology Inc. PS-400-7 solvent purification system or by distillation. Where stated, apparatus was oven dried and purged with nitrogen. Tetrahydrofuran, toluene and *tert*-butanol were dispensed using inert atmosphere techniques.

TLC using polythene or aluminium backed plates pre-coated with Macherey-Nagel Sil G/UV254 nm neutral silica were used to monitor reactions where appropriate. Visualisation of these plates was by 254 nm UV light and/or KMnO₄, ninhydrin or PMA dips followed by gentle warming. TLC data quoted for specific compounds indicate the most suitable method of visualisation. Organic layers were routinely dried with anhydrous MgSO₄ or Na₂SO₄ and concentrated *in vacuo* using a Büchi rotary evaporator. Where necessary, further drying was facilitated by high vacuum. Flash column chromatography was carried out using Davisil LC 60 Å silica gel (35-70 micron) purchased from Fisher or Sigma-Aldrich.

NMR spectra were run in CDCl₃ or *d*₆-DMSO on either a Bruker Avance 250 (250 MHz), Bruker Avance 300 (300 MHz) or Bruker Avance 400 (400 MHz) instrument and recorded at the following frequencies: proton (¹H - 250/300/400 MHz), carbon (¹³C - 75.5 MHz), fluorine (¹⁹F - 376.5 MHz), phosphorus (³¹P - 121.5 MHz). Chemical shifts are reported relative to the residual solvent peak where possible or alternatively to SiMe₄ (δ = 0.00 ppm) as the internal standard. Coupling constants (*J*) are given in Hz and multiplicities denoted as singlet (s), doublet (d), triplet (t), quartet (q), pentet (pent), septet (sep), unresolved multiplet (m), broad (br.) or apparent (app.). All structural assignments were achieved with comparisons from analogous literature compounds where possible. Protons that possess chemical but not magnetic equivalence (AA'BB' systems) as in the case of 1,4-disubstituted aromatics are reported as multiplets or doublets, depending on their appearance in spectra.

Melting points were carried out on a Gallenkamp MF-370 hot stage melting point apparatus and are uncorrected.

IR spectra were recorded neat using a Perkin Elmer Spectrum 100 FT-IR spectrometer (with internal background scan). Absorption maxima (ν_{max}) are

recorded in wavenumbers (cm^{-1}).

Mass spectra, including high resolution spectra, were recorded using electron impact (EI^+) ionisation at the University of Bath using a microTOF electrospray time-of-flight (ESI-TOF) mass spectrometer (Bruker Daltonik GmbH, Bremen, Germany); this was coupled to an Agilent 1200 LC system (Agilent Technologies, Waldbronn, Germany). The LC system was used as an autosampler only. 10 μL of sample were injected into a 30:70 flow of water:acetonitrile at 0.3 mL/min to the mass spectrometer. For each acquisition 10 μL of a calibrant of 5mM sodium formate were injected after the sample.

Unless preparative details are provided, all reagents were commercially available and purchased from Acros Organics, Sigma-Aldrich, Alfa Aesar, Avocado, Fluka, Lancaster, Maybridge or Strem chemical companies.

7.2 Experimental procedures: Chapter 2

7.2.1 Representative Procedure for the Synthesis of Secondary Amines

To an oven-dried, nitrogen purged Young's tube containing $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$ (45.9 mg, 0.075 mmol) and DPEphos (80.8 mg, 0.15 mmol) were added 3-phenyl-1-propanol (408 μL , 3 mmol), amine (3.15 mmol) and toluene (3 mL). The reaction vessel was then sealed and heated to reflux for 24 hours. On completion the reaction was allowed to cool to room temperature and the solvent removed *in vacuo*. Conversion was determined by the disappearance of the characteristic CH_2OH triplet at 3.63 ppm in the ^1H NMR spectra. The crude product was then purified by silica column chromatography.

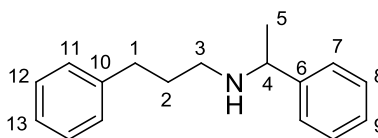
7.2.2 Representative Procedure for the Synthesis of Primary Amines

To an oven-dried, nitrogen purged Young's tube containing $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$ (45.9 mg, 0.075 mmol) and DPEphos (80.8 mg, 0.15 mmol) were added the alcohol (3 mmol), 1-phenethylamine (0.41 mL, 3.15 mmol) and toluene (3 mL). The reaction vessel was then sealed and heated to reflux for 24 hours. On completion the reaction was allowed to cool to room temperature before Pd/C (10 wt%, 10 mol% in Pd), EtOH (11 mL), HCl (6M, 1.1 mL) were added. The atmosphere was then purged with H_2 before the reaction vessel was sealed. The reaction was then heated to 65 $^\circ\text{C}$ for 14

hours. On completion the reaction was allowed to cool to room temperature and filtered through Whatman filter paper grade GF/C before the solvent was removed *in vacuo*. The solid was then recrystallized by dissolving in a minimum of hot EtOH before precipitating with EtOAc.

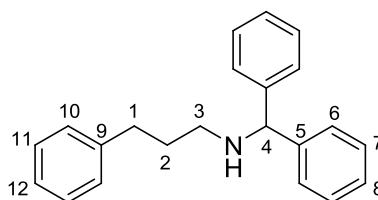
7.2.3 Ruthenium-Catalysed Synthesis of Secondary Amines

3-Phenyl-*N*-(1-phenethyl)propan-1-amine **2.13**



According to representative procedure 7.2.1, the product was purified by silica column chromatography (eluent; EtOAc/hexanes, 2:1, R_f = 0.30, det: KMnO_4) and isolated as a yellow oil (610 mg, 85%). ^1H NMR (300 MHz, CDCl_3 , 25 °C): δ = 7.16-7.36 (10H, m, arom. H), 3.77 (1H, q, J = 6.60 Hz, H_4), 2.45-2.72 (4H, m, H_3 & H_1), 1.76-1.86 (2H, m, H_2), 1.37 (3H, d, J = 6.60 Hz, H_5); ^{13}C NMR (75.4 MHz, CDCl_3 , 25 °C): δ = 145.9 (C_6), 142.3 (C_{10}), 128.5 (C_{12}), 128.5 (C_8), 128.4 (C_{11}), 126.9 (C_9), 126.7 (C_7), 125.8 (C_{13}), 58.4 (C_4), 47.5 (C_3), 33.8 (C_1), 32.0 (C_2), 24.5 (C_5); HRMS(ESI-TOF): calcd. for $\text{C}_{17}\text{H}_{21}\text{NH}^+$: 240.1752. Found: 240.1750 (MH^+). This is consistent with literature data.¹

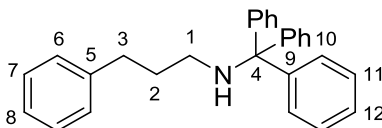
N-Benzhydryl-3-phenylpropan-1-amine **2.14**



According to representative procedure 7.2.1, the product was purified by silica column chromatography (eluent; hexanes/EtOAc, 9:1, R_f = 0.29, det: KMnO_4) and isolated as a yellow oil (714 mg, 79%). IR: $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3060, 3024, 2930, 2855, 1492, 1452, 742, 694; ^1H NMR (300 MHz, CDCl_3 , 25 °C): δ = 7.15-7.41 (15H, m, arom. H), 4.80 (1H, s, H_4), 2.60-2.69 (4H, m, H_3 & H_1), 1.80-1.89 (2H, m, H_2), 1.51 (1H, br s, NH); ^{13}C NMR (75.4 MHz, CDCl_3 , 25 °C): δ = 144.4 (C_5), 142.4 (C_9),

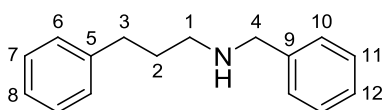
128.6 (C₇), 128.5 (C₁₁), 128.4 (C₁₀), 127.4 (C₆), 127.1 (C₈), 125.8 (C₁₂), 67.6 (C₄), 47.9 (C₃), 33.8 (C₁), 32.1 (C₂); HRMS(ESI-TOF): calcd. for C₂₂H₂₃NH⁺: 302.1909. Found: 302.1897 (MH⁺); CHN: *Anal. Calc.* for C₂₂H₂₃N: C, 87.66%, H, 7.69%, N, 4.65%; Found: C, 87.70%, H, 7.63%, N, 4.66%.

3-Phenyl-*N*-tritylpropan-1-amine **2.15**



According to representative procedure 7.2.1, the product was purified by silica column chromatography (eluent; CH₂Cl₂/hexanes, 1:1, R_f = 0.25, det: KMnO₄) and isolated as a colourless solid (680 mg, 60%). M. p. = 88-90 °C; IR: ν_{max}/cm⁻¹ (neat) 3057, 3019, 2938, 2844, 1594, 1488, 1453, 1211, 1184, 1150, 1030; ¹H NMR (300 MHz, CDCl₃, 25 °C): δ = 7.45-7.49 (6H, m, H₁₁), 7.14-7.30 (14H, m, arom. H), 2.66 (2H, t, *J* = 7.95 Hz, H₃), 2.21 (2H, t, *J* = 6.75 Hz, H₁), 1.77-1.86 (2H, m, H₂), 1.53 (1H, br s, NH); ¹³C NMR (75.4 MHz, CDCl₃, 25 °C): δ = 146.4 (C₉), 142.5 (C₅), 128.8 (C₁₁), 128.4 (C₆ & C₇), 127.9 (C₁₀), 126.3 (C₁₂), 125.8 (C₈), 71.0 (C₄), 43.4 (C₁), 33.9 (C₃), 32.7 (C₂); HRMS(ESI-TOF): calcd. for C₂₇H₂₇NH⁺: 378.2216. Found: 378.2193 (MH⁺), 400.2021 (MNa⁺); CHN: *Anal. Calc.* for C₂₇H₂₇N: C, 89.08%, H, 7.21%, N, 3.71%; Found: C, 89.20%, H, 7.25%, N, 3.66%.

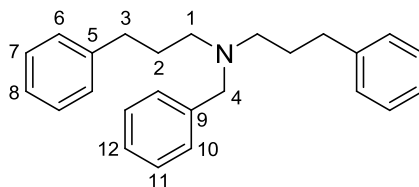
N-Benzyl-3-phenylpropan-1-amine **2.16**



According to representative procedure 7.2.1, the product was purified by silica column chromatography (eluent; Et₂O/petroleum ether b. p. 40-60 °C, 3:2, R_f = 0.22, det: KMnO₄) and isolated as a brown oil (385 mg, 57%). ¹H NMR (300 MHz, CDCl₃, 25 °C): δ = 7.23-7.33 (7H, m, arom. H), 7.16-7.20 (3H, m, arom. H), 3.79 (2H, s, H₄), 2.64-2.71 (4H, m, H₁ & H₃), 1.81-1.91 (2H, m, H₂); ¹³C NMR (75.4 MHz, CDCl₃, 25 °C): δ = 142.3 (C₅), 140.5 (C₉), 128.5 (C₇ & C₁₁), 128.4 (C₆), 128.3 (C₁₀), 127.0 (C₁₂), 125.9 (C₈), 54.1 (C₁), 49.0 (C₄), 33.7 (C₃), 31.8 (C₂); HRMS(ESI-TOF): calcd. for

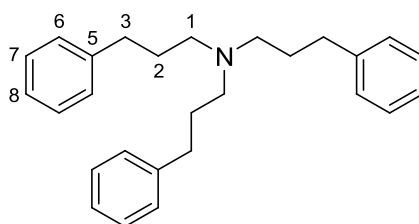
$\text{C}_{16}\text{H}_{19}\text{NH}^+$: 226.3362. Found: 226.1712 (MH^+). This is consistent with literature data.²

N-Benzyl-3-phenyl-*N*-(3-phenylpropyl)propan-1-amine **2.18**

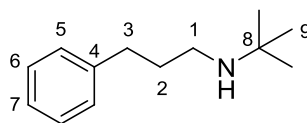


According to representative procedure 7.2.1, the product was purified by silica column chromatography (eluent; petroleum ether b. p. 40-60 °C/ Et_2O , 9:1, R_f = 0.24, det: KMnO_4) and isolated as a yellow oil (340 mg, 33%). ^1H NMR (300 MHz, CDCl_3 , 25 °C): δ = 7.15-7.37 (15H, m, arom. H), 3.60 (2H, s, H_4), 2.63 (4H, t, J = 7.50 Hz, H_3), 2.51 (4H, t, J = 7.20 Hz, H_1), 1.76-1.86 (4H, m, H_2); ^{13}C NMR (75.4 MHz, CDCl_3 , 25 °C): δ = 142.7 (C_5), 140.1 (C_9), 129.0 (C_{10}), 128.5 (C_7), 128.4 (C_6), 128.3 (C_{11}), 126.8 (C_{12}), 125.8 (C_8), 58.8 (C_4), 53.4 (C_1), 33.8 (C_3), 29.1 (C_2); HRMS(ESI-TOF): calcd. for $\text{C}_{25}\text{H}_{29}\text{NH}^+$: 344.2373. Found: 344.2509 (MH^+). This is consistent with literature data.³

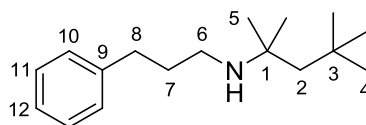
Tris(3-phenylpropyl)amine **2.19**



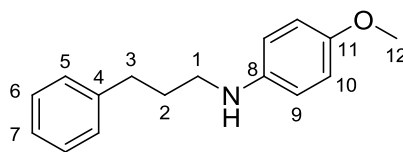
According to representative procedure 7.2.1, the product was purified by silica column chromatography (eluent; petroleum ether b. p. 40-60 °C/ Et_2O , 2:1, R_f = 0.24, det: KMnO_4) and isolated as a yellow oil (100 mg, 9%). ^1H NMR (300 MHz, CDCl_3 , 25 °C): δ = 7.19-7.38 (15H, m, arom. H), 2.65 (6H, t, J = 7.50 Hz, H_3), 2.52 (6H, t, J = 7.2 Hz, H_1), 1.74-1.84 (6H, m, H_2); ^{13}C NMR (75.4 MHz, CDCl_3 , 25 °C): δ = 142.6 (C_5), 128.5 (C_7), 127.1 (C_6), 125.8 (C_8), 53.7 (C_1), 33.9 (C_3), 29.0 (C_2); HRMS(ESI-TOF): calcd. for $\text{C}_{27}\text{H}_{33}\text{NH}^+$: 372.2686. Found: 372.2802 (MH^+). This is consistent with literature data.⁴

N-*tert*-Butyl-3-phenylpropan-1-amine **2.32**

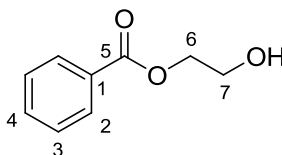
According to representative procedure 7.2.1, the product was purified by silica column chromatography (eluent; CH₂Cl₂/MeOH, 9:1, R_f = 0.15, det: KMnO₄) and isolated as a brown oil (350 mg, 61%). ¹H NMR (300 MHz, CDCl₃, 25 °C): δ = 7.25-7.30 (2H, m, arom. H), 7.15-7.22 (3H, m, arom. H), 2.66 (2H, t, *J* = 7.20 Hz, H₃), 2.60 (2H, t, *J* = 7.50 Hz, H₁), 1.77-1.87 (2H, m, H₂), 1.10 (9H, s, H₉); ¹³C NMR (75.4 MHz, CDCl₃, 25 °C): δ = 142.2 (C₄), 128.5 (C₆), 128.4 (C₅), 125.9 (C₇), 50.7 (C₈), 42.2 (C₁), 33.9 (C₃), 32.5 (C₂), 29. (C₉); HRMS(ESI-TOF): calcd. for C₁₃H₂₁NH⁺ : 192.1752. Found: 192.1717 (MH⁺). This is consistent with literature data.⁵

2,4,4-Trimethyl-*N*-(3-phenylpropyl)pentan-2-amine **2.33**

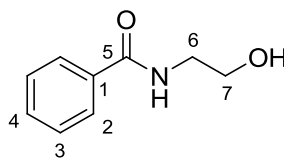
According to representative procedure 7.2.1, the product was purified by silica column chromatography (eluent; Et₂O/petroleum ether b. p. 40-60 °C, 2:1, R_f = 0.20, det: KMnO₄) and isolated as a brown oil (661 mg, 89%). IR: ν_{max}/cm⁻¹ (neat) 2951, 1476, 1454, 1363, 1229, 743, 697; ¹H NMR (300 MHz, CDCl₃, 25 °C): δ = 7.25-7.30 (2H, m, arom. H), 7.15-7.20 (3H, m, arom. H), 2.66 (2H, t, *J* = 7.50 Hz, H₈), 2.59 (2H, t, *J* = 7.20 Hz, H₆), 1.73-1.83 (2H, m, H₇), 1.43 (2H, s, H₂), 1.14 (6H, s, H₅), 1.00 (9H, s, H₄); ¹³C NMR (75.4 MHz, CDCl₃, 25 °C): δ = 142.5 (C₉), 128.5 (C₁₁), 128.4 (C₁₀), 125.8 (C₁₂), 54.3 (C₁), 53.2 (C₂), 41.7 (C₆), 34.0 (C₈), 32.9 (C₇), 31.9 (C₄), 31.8 (C₃), 29.1 (C₅); HRMS(ESI-TOF): calcd. for C₁₇H₂₉NH⁺ : 248.2378. Found: 248.2363 (MH⁺); CHN: *Anal. Calc.* for C₁₇H₂₉N: C, 82.52%, H, 11.81%, N, 5.66%; Found: C, 82.40%, H, 11.90%, N, 5.61%.

4-Methoxy-*N*-(3-phenylpropyl)aniline **2.34**

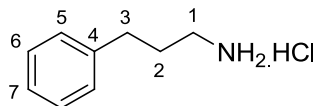
According to representative procedure 7.2.1, the product was purified by silica column chromatography (eluent; petroleum ether b. p. 40-60 °C/Et₂O, 5:1, *R_f* = 0.17, det: KMnO₄) and isolated as a yellow oil (432 mg, 60%). ¹H NMR (300 MHz, CDCl₃, 25 °C): δ = 7.30-7.35 (2H, m, arom. H), 7.20-7.24 (3H, m, arom. H), 6.81 (2H, d, *J* = 9.00 Hz, H₁₀), 6.59 (2H, d, *J* = 9.00 Hz, H₉), 3.78 (3H, s, H₁₂), 3.14 (2H, t, *J* = 6.90 Hz, H₁), 2.77 (2H, t, *J* = 7.50 Hz, H₃), 1.93-2.02 (2H, m, H₂); ¹³C NMR (75.4 MHz, CDCl₃, 25 °C): δ = 152.2 (C₁₁), 142.8 (C₄), 141.9 (C₈), 128.5 (C₅ & C₆), 126.0 (C₇), 115.0 (C₁₀), 114.2 (C₉), 55.9 (C₁₂), 44.6 (C₁), 33.6 (C₃), 31.3 (C₂); HRMS(ESI-TOF): calcd. for C₁₆H₁₉NH⁺: 242.1539. Found: 242.1665 (MH⁺). This is consistent with literature data.¹

2-Hydroxyethyl benzoate **2.42**

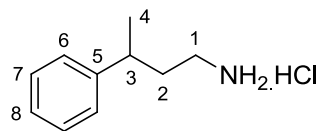
Benzoyl chloride (2.9 mL, 25 mmol) was added to an ice cooled solution of ethylene glycol (4.2 mL, 75 mmol) and pyridine (2.25 mL, 28 mmol) in CH₂Cl₂ (25 mL). The reaction was allowed to warm to room temperature before leaving to stir for 26 hours. The reaction was then concentrated *in vacuo* before purifying by silica column chromatography (eluent; hexanes/EtOAc, 2:1, *R_f* = 0.23, det: KMnO₄) and isolated as a colourless solid (2.70 g, 65%). ¹H NMR (300 MHz, CDCl₃, 25 °C): δ = 8.06 (2H, dd, *J* = 8.40, 1.50 Hz, H₂), 7.58 (1H, tt, *J* = 7.35, 1.50 Hz, H₄), 7.42-7.48 (2H, m, H₃), 4.47 (2H, t, *J* = 4.65 Hz, H₆), 3.97 (2H, t, *J* = 4.65 Hz, H₇), 2.12 (1H, br s, OH); ¹³C NMR (75.4 MHz, CDCl₃, 25 °C): δ = 167.9 (C₅), 133.3 (C₁), 129.9 (C₄), 129.8 (C₃), 128.5 (C₂), 66.8 (C₆), 61.4 (C₇); HRMS(ESI-TOF): calcd. for C₉H₁₀O₃H⁺: 167.0708. Found: 167.0707 (MH⁺), 189.0525 (MNa⁺). This is consistent with literature data.⁶

N-(2-Hydroxyethyl)benzamide **2.43**

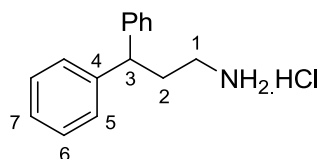
Benzoyl chloride (2.9 mL, 25 mmol) was added to an ice cooled solution of ethanolamine (3.7 mL, 62.5 mmol) in CH_2Cl_2 (25 mL) dropwise. The reaction was then left to stir for 2 hours before H_2O (10 mL). The mixture was then acidified with HCl (6 M). The organic layer was then separated and washed with HCl (2 M, 2 x 15 mL). The organic layer was then dried (MgSO_4) and concentrated *in vacuo*. The product (1.36 g, 33%) was isolated as a colourless solid. ^1H NMR: (CDCl_3 , 300 MHz) δ = 7.72 (2H, dd, J = 8.40, 1.50 Hz, H_2), 7.33-7.47 (3H, m, H_3 & H_4), 6.61 (1H, br s, NH), 3.77 (2H, app. t, J = 4.95 Hz, H_7), 3.54-3.59 (2H, m, H_6), 2.67 (1H, br s, OH); ^{13}C NMR: (CDCl_3 , 75.4 MHz) δ = 168.8 (C_5), 134.2 (C_1), 131.7 (C_4), 128.7 (C_3), 127.1 (C_2), 62.1 (C_7), 42.9 (C_6); HRMS(ESI-TOF): calcd. for $\text{C}_9\text{H}_{11}\text{NO}_2\text{H}^+$: 166.0868. Found: 166.0866 (MH^+), 188.0678 (MNa^+). This is consistent with literature data.⁷

3-Phenylpropan-1-amine hydrochloride **2.44**

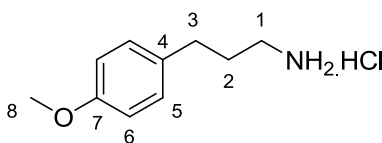
According to representative procedure 7.2.2, the product was isolated as colourless crystalline solid (438 mg, 85%). ^1H NMR (300 MHz, $\text{DMSO}-d_6$, 25 °C): δ = 8.11 (3H, br s, NH_3^+), 7.28-7.37 (2H, m, arom. H_6), 7.17-7.23 (3H, m, arom. H), 2.75 (2H, t, J = 7.80 Hz, H_1), 2.64 (2H, t, J = 7.80 Hz, H_3), 1.81-1.91 (2H, m, H_2); ^{13}C NMR (75.4 MHz, $\text{DMSO}-d_6$, 25 °C): δ = 140.9 (C_4), 128.4 (C_6), 128.2 (C_5), 125.9 (C_7), 38.2 (C_1), 31.8 (C_2), 28.6 (C_3); HRMS(ESI-TOF): calcd. for $\text{C}_9\text{H}_{13}\text{NH}^+$: 136.1126. Found: 136.1123 (MH^+). This is consistent with literature data.⁸

3-Phenylbutan-1-amine hydrochloride **2.45**

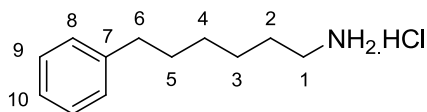
According to representative procedure 7.2.2, the product was isolated as colourless crystalline solid (323 mg, 58%). ^1H NMR (300 MHz, $\text{DMSO-}d_6$, 25 °C): δ = 7.88 (3H, br s, NH_3^+), 7.18 – 7.35 (5H, m, arom. H), 2.80 (1H, q, J = 6.90 Hz, H_3), 2.65 – 2.74 (1H, m, H_2), 2.53 – 2.57 (1H, m, H_2), 1.82 (2H, q, J = 7.80 Hz, H_1), 1.21 (3H, d, J = 6.90 Hz, H_4); ^{13}C NMR (75.4 MHz, $\text{DMSO-}d_6$, 25 °C): δ = 145.8 (C_5), 128.5 (C_7), 126.8 (C_6), 126.2 (C_8), 37.3 (C_1), 36.4 (C_2), 35.0 (C_3), 22.0 (C_4); HRMS(ESI-TOF): calcd. for $\text{C}_{10}\text{H}_{15}\text{NH}^+$: 150.1283. Found: 150.1276 (MH^+). This is consistent with literature data.⁹

3,3-Diphenylpropan-1-amine hydrochloride **2.46**

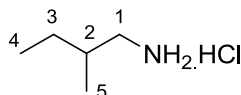
According to representative procedure 7.2.2, the product was isolated as colourless crystalline solid (557 mg, 75%). ^1H NMR (300 MHz, $\text{DMSO-}d_6$, 25 °C): δ = 8.08 (3H, br s, NH_3^+), 7.18 – 7.31 (10H, m, arom. H), 4.11 (1H, t, J = 7.80 Hz, H_3), 2.63 (2H, t, J = 7.65 Hz, H_1), 2.29 – 2.36 (2H, m, H_2); ^{13}C NMR (75.4 MHz, $\text{DMSO-}d_6$, 25 °C): δ = 143.9 (C_4), 128.5 (C_6), 127.4 (C_5), 126.3 (C_7), 47.2 (C_3), 37.5 (C_1), 32.3 (C_2); HRMS(ESI-TOF): calcd. for $\text{C}_{15}\text{H}_{17}\text{NH}^+$: 212.1439. Found: 212.1430 (MH^+). This is consistent with literature data.⁹

3-(4-Methoxyphenyl)propan-1-amine hydrochloride **2.47**

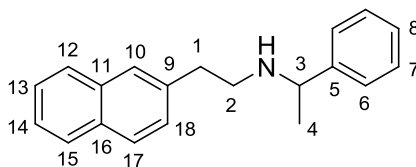
According to representative procedure 7.2.2, the product was isolated as colourless crystalline solid (454 mg, 54%). ^1H NMR (300 MHz, $\text{DMSO-}d_6$, 25 °C): δ = 7.81 (3H, br s, NH_3^+), 7.12 (2H, d, J = 8.55 Hz, H_5), 6.86 (2H, d, J = 8.55 Hz, H_6), 3.72 (3H, s, H_8), 2.75 (2H, t, J = 7.65 Hz, H_1), 2.57 (2H, t, J = 7.65 Hz, H_3), 1.80 (2H, m, H_2); ^{13}C NMR (75.4 MHz, $\text{DMSO-}d_6$, 25 °C): δ = 157.6 (C_7), 132.7 (C_4), 129.2 (C_5), 113.8 (C_6), 55.0 (C_8), 38.2 (C_1), 31.0 (C_2), 28.9 (C_3); HRMS(ESI-TOF): calcd. for $\text{C}_{10}\text{H}_{15}\text{NOH}^+$: 166.1232. Found: 166.1221 (MH^+). This is consistent with literature data.¹⁰

6-Phenylhexan-1-amine hydrochloride **2.48**

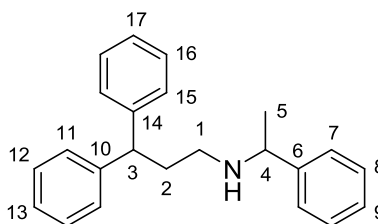
According to representative procedure 7.2.2, the product was isolated as colourless crystalline solid (417 mg, 65%). ^1H NMR (300 MHz, $\text{DMSO-}d_6$, 25 °C): δ = 7.85 (3H, br s, NH_3^+), 7.14-7.30 (5H, m, arom. H), 2.73 (2H, t, J = 7.50 Hz, H_1), 2.57 (2H, t, J = 7.65 Hz, H_6), 1.49-1.61 (4H, m, H_2 & H_5), 1.26-1.38 (4H, m, H_3 & H_4); ^{13}C NMR (75.4 MHz, $\text{DMSO-}d_6$, 25 °C): δ = 142.1 (C_{10}), 128.2 (C_8), 128.2 (C_9), 125.6 (C_7), 38.6 (C_1), 34.9 (C_6), 30.7 (C_2), 28.1 (C_5), 26.7 (C_4), 25.6 (C_3); HRMS(ESI-TOF): calcd. for $\text{C}_{12}\text{H}_{19}\text{NH}^+$: 178.1596. Found: 178.1589 (MH^+). This is consistent with literature data.¹¹

2-Methylbutan-1-amine hydrochloride **2.49**

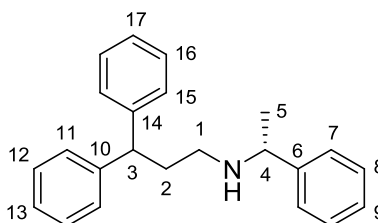
According to representative procedure 7.2.2, the product was isolated as colourless crystalline solid (248 mg, 67%). ^1H NMR (300 MHz, D_2O , 25 °C): δ = 4.45 (3H, br s, NH_3^+), 2.58 (1H, dd, J = 12.60 6.30 Hz, H_1), 2.41 (1H, dd, J = 12.60 7.80 Hz, H_1), 1.28-1.41 (1H, m, H_2), 0.96-1.10 (1H, m, H_3), 0.78-0.93 (1H, m, H_3), 0.58 (3H, d, J = 6.90 Hz, H_5), 0.51 (3H, t, J = 7.20 Hz, H_4); ^{13}C NMR (75.4 MHz, D_2O , 25 °C): δ = 45.0 (C_1), 32.8 (C_2), 26.3 (C_3), 16.1 (C_5), 10.4 (C_4); HRMS(ESI-TOF): calcd. for $\text{C}_5\text{H}_{12}\text{NH}^+$: 87.1048. Found: 87.1059 (MH^+). This is consistent with literature data.¹²

2-(Naphthalen-2-yl)-*N*-(1-phenylethyl)ethanamine **2.50**

According to representative procedure 7.2.1, the product was purified by silica column chromatography (eluent; hexanes/EtOAc, 2:1, R_f = 0.20, det: KMnO_4) and isolated as a brown oil (653 mg, 79%). IR: $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3052, 3024, 2958, 2856, 1633, 1600, 1508, 1492, 1450, 1367, 1124; ^1H NMR (300 MHz, CDCl_3 , 25 °C): δ = 7.75-7.82 (3H, m, arom. H), 7.61 (1H, br s, H_{10}), 7.40-7.49 (2H, m, arom. H), 7.20-7.34 (6H, m, arom. H), 3.80 (1H, q, J = 6.60 Hz, H_3), 2.79-2.98 (4H, m, H_1 & H_2), 1.49 (1H, br s, NH), 1.33 (3H, d, J = 6.60 Hz, H_4); ^{13}C NMR (75.4 MHz, CDCl_3 , 25 °C): δ = 145.7 (C_5), 137.7 (C_9), 133.7 (C_{11}), 132.3 (C_{16}), 128.5 (C_7), 128.1 (C_{10}), 127.7 (C_{18}), 127.6 (C_{15}), 127.4 (C_{12}), 127.1 (C_{17}), 127.0 (C_8), 126.7 (C_6), 126.1 (C_{13}), 125.4 (C_{14}), 58.4 (C_3), 48.8 (C_2), 36.7 (C_1), 24.5 (C_4); HRMS(ESI-TOF): calcd. for $\text{C}_{20}\text{H}_{21}\text{NH}^+$: 276.1752. Found: 276.1730 (MH^+); CHN: *Anal. Calc.* for $\text{C}_{20}\text{H}_{21}\text{N}$: C, 87.23%, H, 7.69%, N, 5.09%; Found: C, 87.30%, H, 7.75%, N, 4.96%.

3,3-diphenyl-*N*-(1-phenethyl)propan-1-amine (Fendiline) **2.52**

According to representative procedure 7.2.1, the product was purified by silica column chromatography (eluent; hexanes/EtOAc, 2:1, R_f = 0.21, det: KMnO_4) and isolated as a brown oil (672 mg, 71%). ^1H NMR (300 MHz, CDCl_3 , 25 °C): δ = 7.12-7.32 (15H, m, arom. H), 3.97 (1H, t, J = 7.65 Hz, H_3), 3.68 (1H, q, J = 6.60 Hz, H_4), 2.40-2.52 (2H, m, H_1), 2.15-2.28 (2H, m, H_2), 1.46 (1H, br s, NH), 1.30 (3H, d, J = 6.60 Hz, H_5); ^{13}C NMR (75.4 MHz, CDCl_3 , 25 °C): δ = 145.8 (C_6), 145.1 (C_{10}), 144.8 (C_{14}), 128.5 (C_{12} & C_{16}), 128.5 (C_8), 128.0 (C_{11}), 127.8 (C_{15}), 126.9 (C_9), 126.6 (C_7), 126.2 (C_{13}), 126.2 (C_{17}), 58.2 (C_4), 49.1 (C_3), 46.1 (C_1), 36.1 (C_2), 25.5 (C_5); HRMS(ESI-TOF): calcd. for $\text{C}_{23}\text{H}_{25}\text{NH}^+$: 316.2065. Found: 316.2051 (MH^+). This is consistent with literature data.¹³

(*R*)-3,3-diphenyl-*N*-(1-phenethyl)propan-1-amine ((*R*)-Fendiline) **2.56**

According to representative procedure 7.2.1, the product was purified by silica column chromatography (eluent; hexanes/EtOAc, 2:1, R_f = 0.21, det: KMnO_4) and isolated as a brown oil (672 mg, 71%). $[\alpha]_D^{26}$: +12.0° (c 0.5, CHCl_3); ^1H NMR (300 MHz, CDCl_3 , 25 °C): δ = 7.12-7.32 (15H, m, arom. H), 3.97 (1H, t, J = 7.65 Hz, H_3), 3.68 (1H, q, J = 6.60 Hz, H_4), 2.40-2.52 (2H, m, H_1), 2.15-2.28 (2H, m, H_2), 1.46 (1H, br s, NH), 1.30 (3H, d, J = 6.60 Hz, H_5); ^{13}C NMR (75.4 MHz, CDCl_3 , 25 °C): δ = 145.8 (C_6), 145.1 (C_{10}), 144.8 (C_{14}), 128.5 (C_{12} & C_{16}), 128.5 (C_8), 128.0 (C_{11}), 127.8 (C_{15}), 126.9 (C_9), 126.6 (C_7), 126.2 (C_{13}), 126.2 (C_{17}), 58.2 (C_4), 49.1 (C_3), 46.1 (C_1), 36.1 (C_2), 25.5 (C_5); HRMS(ESI-TOF): calcd. for $\text{C}_{23}\text{H}_{25}\text{NH}^+$: 316.2065. Found: 316.2051 (MH^+). This is consistent with literature data.¹⁴

7.2.3 Representative Procedure for the Determination of Chirality via ^1H NMR using (*S*)-O-Acetylmandelic acid

To a vial containing (*S*)-O-Acetylmandelic acid (19.4 mg, 0.1 mmol) was added the amine (0.1 mmol) and CDCl_3 (0.6 mL). The sample was then shaken and analysed by ^1H NMR.

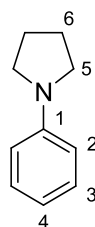
7.3 Experimental procedures: Chapter 3

7.3.1 Representative Procedure for the Synthesis of Cyclic Tertiary Amines from Primary Amines and Diols

To an oven-dried, nitrogen purged Young's tube containing $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$ (45.9 mg, 0.075 mmol) and DPEphos (80.8 mg, 0.15 mmol) were added the amine (3 mmol), diol (3.6 mmol), triethylamine (42 μL , 0.3 mmol) and toluene (3 mL). The reaction vessel was then sealed and heated to reflux for 24 hours. On completion the reaction was allowed to cool to room temperature and the solvent removed *in vacuo*. The crude product was then purified by silica column chromatography.

7.3.2 Ruthenium-Catalysed Synthesis of Cyclic Tertiary Amines from Primary Alcohols and Diols

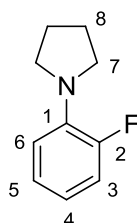
1-Phenylpyrrolidine 3.3



According to representative procedure 7.3.1, the product was purified by silica column chromatography (eluent; hexanes/EtOAc, 20:1, R_f = 0.52, det: KMnO_4) and isolated as a yellow oil (344 mg, 78%). ^1H NMR: (CDCl_3 , 300 MHz) δ = 7.27 (2H, dd, J = 8.85 7.35 Hz, H_3), 6.70 (1H, tt, J = 7.35 1.05 Hz, H_4), 6.61 (2H, dd, J = 8.85 1.05 Hz, H_2), 3.30-3.34 (4H, m, H_5), 2.01-2.06 (4H, m, H_6); ^{13}C NMR: (CDCl_3 , 75.4

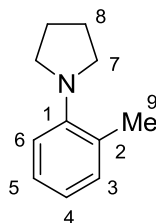
MHz) δ = 148.0 (C₁), 129.1 (C₃), 115.3 (C₂), 111.6 (C₄), 47.5 (C₅), 25.4 (C₆); HRMS(ESI-TOF): calcd. For C₁₀H₁₃NH⁺: 148.1126. Found: 148.1129 (MH⁺). This is consistent with literature data.¹⁵

1-(2-Fluorophenyl)pyrrolidine **3.4**



According to representative procedure 7.3.1, the product was purified by silica column chromatography (eluent; hexanes/EtOAc, 20:1, R_f = 0.65, det: KMnO₄) and isolated as a colourless oil (165 mg, 33%). IR: $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3065, 2966, 2874, 2824, 1613, 1504, 1487, 1358, 1204; ¹H NMR: (CDCl₃, 300 MHz) δ = 6.95-7.03 (2H, m, H₃ & H₅), 6.63-6.72 (2H, m, H₄ & H₆), 3.37-3.43 (4H, m, H₇), 1.94-1.99 (4H, m, H₈); ¹³C NMR: (CDCl₃, 75.4 MHz) δ = 152.4 (d, J = 152.4 Hz, C₂), 137.6 (d, J = 9.3 Hz, C₁), 124.5 (d, J = 3.0 Hz, C₅), 117.3 (d, J = 7.2 Hz, C₄), 116.2 (d, J = 21.0 Hz, C₃), 115.4 (d, J = 5.1 Hz, C₆), 49.9 (d, J = 5.0 Hz, C₇), 25.3 (d, J = 1.8 Hz, C₈); ¹⁹F NMR: (CDCl₃, 376 MHz) δ = -126.9 (s); HRMS(ESI-TOF): calcd. for C₁₀H₁₂NFH⁺: 166.1032. Found: 166.1032 (MH⁺); CHN: *Anal. Calc.* for C₁₀H₁₂NF: C, 72.70%, H, 7.32%, N, 8.48%; Found: C, 72.60%, H, 7.34%, N, 8.52%.

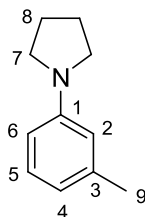
1-*o*-Tolylpyrrolidine **3.6**



According to representative procedure 7.3.1, the product was purified by silica column chromatography (eluent; hexanes/EtOAc, 20:1, R_f = 0.25, det: KMnO₄) and isolated as a yellow oil (368 mg, 76%). ¹H NMR: (CDCl₃, 300 MHz) δ = 7.10-7.14 (2H, m, H₃ & H₅), 6.90 (1H, dd, J = 9.00, 1.20 Hz, H₆), 6.84 (1H, dt, J = 7.35, 1.10

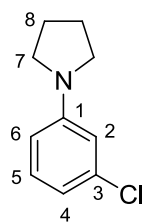
Hz, H₄), 3.18 (4H, m, H₇), 2.34 (3H, s, H₉), 1.92-1.96 (4H, m, H₈); ¹³C NMR: (CDCl₃, 75.4 MHz) δ = 149.6 (C₁), 131.8 (C₃), 128.9 (C₅), 126.4 (C₂), 120.4 (C₄), 115.9 (C₆), 51.1 (C₇), 25.1 (C₈), 20.7 (C₉); HRMS(ESI-TOF): calcd. for C₁₁H₁₅NH⁺: 162.1283. Found: 162.1279 (MH⁺). This is consistent with literature data.¹⁶

1-*m*-Tolylpyrrolidine **3.9**



According to representative procedure 7.3.1, the product was purified by silica column chromatography (eluent; hexanes/EtOAc, 20:1, R_f = 0.37, det: KMnO₄) and isolated as a yellow oil (455 mg, 94%). ¹H NMR: (CDCl₃, 300 MHz) δ = 7.12 (1H, dd, *J* = 8.85 7.50 Hz, H₅), 6.50 (1H, d, *J* = 7.50 Hz, H₄), 6.41 (2H, br s, H₂ & H₆), 3.26-3.30 (4H, m, H₇), 2.32 (3H, s, H₉), 1.97-2.01 (4H, m, H₈); ¹³C NMR: (CDCl₃, 75.4 MHz) δ = 148.1 (C₁), 138.7 (C₃), 128.9 (C₅), 116.3 (C₄), 112.3 (C₂), 108.9 (C₆), 47.5 (C₇), 25.4 (C₈), 21.8 (C₉); HRMS(ESI-TOF): calcd. for C₁₁H₁₅NH⁺: 162.1283. Found: 162.1278 (MH⁺). This is consistent with literature data.¹⁶

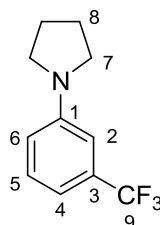
1-(3-Chlorophenyl)pyrrolidine **3.10**



According to representative procedure 7.3.1, the product was purified by silica column chromatography (eluent; hexanes/EtOAc, 20:1, R_f = 0.41, det: KMnO₄) and isolated as a yellow oil (456 mg, 84%). ¹H NMR: (CDCl₃, 300 MHz) δ = 7.11 (1H, t, *J* = 8.10 Hz, H₅), 6.61 (1H, ddd, *J* = 8.10 2.10 0.90 Hz, H₄), 6.52 (1H, t, *J* = 2.10 Hz, H₂), 6.42 (1H, ddd, *J* = 8.10 2.10 0.90 Hz, H₆), 3.24-3.29 (4H, m, H₇), 1.98-2.03 (4H, m, H₈); ¹³C NMR: (CDCl₃, 75.4 MHz) δ = 148.8 (C₁), 134.9 (C₃), 129.9 (C₅), 115.1 (C₄), 111.4 (C₂), 109.8 (C₆), 47.5 (C₇), 25.4 (C₈); HRMS(ESI-TOF): calcd. for

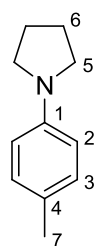
$\text{C}_{10}\text{H}_{12}\text{NClH}^+$: 182.0737. Found: 182.0719 (MH^+). This is consistent with literature data.¹⁷

1-(3-(Trifluoromethyl)phenyl)pyrrolidine **3.11**



According to representative procedure 7.3.1, the product was purified by silica column chromatography (eluent; hexanes/EtOAc, 20:1, R_f = 0.42, det: KMnO_4) and isolated as a colourless oil (387 mg, 60%). ^1H NMR: (CDCl_3 , 300 MHz) δ = 7.26-7.32 (1H, m, H_5), 6.88 (1H, d, J = 7.50 Hz, H_4), 6.74 (1H, s, H_2), 6.68 (1H, d, J = 8.25 Hz, H_6), 3.29-3.33 (4H, m, H_7), 2.01 – 2.06 (4H, m, H_8); ^{13}C NMR: (CDCl_3 , 75.4 MHz) δ = 148.0 (C_1), 131.5 (d, J = 31.4 Hz, C_3), 129.6 (C_5), 124.8 (d, J = 272.1 Hz, C_9), 114.7, (d, J = 1.1 Hz, C_6), 111.7 (q, J = 3.9 Hz, C_4), 107.9 (q, J = 4.0 Hz, C_2), 47.7 (C_7), 25.6 (C_8); HRMS(ESI-TOF): calcd. for $\text{C}_{11}\text{H}_{12}\text{NF}_3\text{H}^+$: 216.0998. Found: 216.1000 (MH^+). This is consistent with literature data.¹⁸

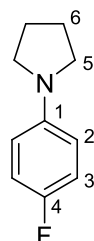
1-*p*-Tolylpyrrolidine **3.13**



According to representative procedure 7.3.1, the product was purified by silica column chromatography (eluent; hexanes/EtOAc, 20:1, R_f = 0.45, det: KMnO_4) and isolated as a colourless crystalline solid (314 mg, 65%). ^1H NMR: (CDCl_3 , 300 MHz) δ = 7.04 (2H, d, J = 8.40 Hz, H_3), 6.51 (2H, d, J = 8.40 Hz, H_2), 3.24-3.28 (4H, m, H_5), 2.26 (3H, s, H_7), 1.97-2.01 (4H, m, H_6); ^{13}C NMR: (CDCl_3 , 75.4 MHz) δ = 146.1 (C_1), 129.6 (C_3), 124.4 (C_4), 111.7 (C_2), 47.8 (C_5), 25.4 (C_6), 20.2 (C_7); HRMS(ESI-

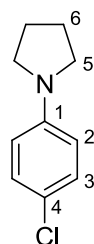
TOF): calcd. For $C_{11}H_{15}NH^+$: 162.1283. Found: 162.1286 (MH^+). This is consistent with literature data.¹⁶

1-(4-Fluorophenyl)pyrrolidine **3.14**

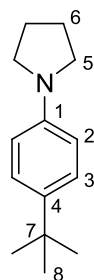


According to representative procedure 7.3.1, the product was purified by silica column chromatography (eluent; hexanes/EtOAc, 20:1, R_f = 0.31, det: $KMnO_4$) and isolated as a yellow oil (387 mg, 78%). 1H NMR: ($CDCl_3$, 300 MHz) δ = 6.94 (2H, t, J = 8.85 Hz, H_3), 6.48 (2H, q, J = 4.50 Hz, H_2), 3.22-3.27 (4H, m, H_5), 1.98-2.03 (4H, m, H_6); ^{13}C NMR: ($CDCl_3$, 75.4 MHz) δ = 154.8 (d, J = 232.84 Hz, C_4), 144.8 (d, J = 1.28 Hz, C_1), 115.4 (d, J = 22.02 Hz, C_3), 112.0 (d, J = 7.16 Hz, C_2), 48.1 (C_5), 25.4 (C_6); HRMS(ESI-TOF): calcd. for $C_{10}H_{12}NFH^+$: 166.1032. Found: 166.1030 (MH^+). This is consistent with literature data.¹⁹

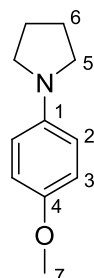
1-(4-Chlorophenyl)pyrrolidine **3.15**



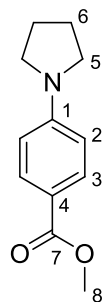
According to representative procedure 7.3.1, the product was purified by silica column chromatography (eluent; hexanes/EtOAc, 20:1, R_f = 0.29, det: $KMnO_4$) and isolated as a colourless solid (474 mg, 87%). 1H NMR: ($CDCl_3$, 300 MHz) δ = 7.16 (2H, d, J = 9.00 Hz, H_2), 6.47 (2H, d, J = 9.00 Hz, H_3), 3.23-3.28 (4H, m, H_5), 1.99-2.04 (4H, m, H_6); ^{13}C NMR: ($CDCl_3$, 75.4 MHz) δ = 146.5 (C_1), 128.8 (C_3), 120.0 (C_2), 112.6 (C_4), 47.7 (C_5), 25.4 (C_6); HRMS(ESI-TOF): calcd. For $C_{10}H_{12}NClH^+$: 182.0737. Found: 182.0722 (MH^+). This is consistent with literature data.²⁰

1-(4-*tert*-Butylphenyl)pyrrolidine **3.16**

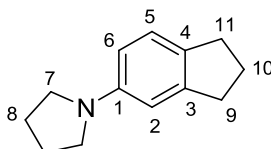
According to representative procedure 7.3.1, the product was purified by silica column chromatography (eluent; hexanes/EtOAc, 20:1, $R_f = 0.31$, det: KMnO_4) and isolated as a yellow oil (518 mg, 85%). ^1H NMR: (CDCl_3 , 300 MHz) $\delta = 7.32$ (2H, d, $J = 8.85$ Hz, H_3), 6.59 (2H, d, $J = 8.85$ Hz, H_2), 3.30-3.35 (4H, m, H_5), 2.01-2.05 (4H, m, H_6), 1.35 (9H, s, H_8); ^{13}C NMR: (CDCl_3 , 75.4 MHz) $\delta = 145.9$ (C_1), 137.9 (C_4), 125.9 (C_3), 111.3 (C_2), 47.7 (C_5), 33.7 (C_7), 31.6 (C_8), 25.4 (C_6); HRMS(ESI-TOF): calcd. for $\text{C}_{14}\text{H}_{21}\text{NH}^+$: 204.1752. Found: 204.1747 (MH^+). This is consistent with literature data.²¹

1-(4-Methoxyphenyl)pyrrolidine **3.17**

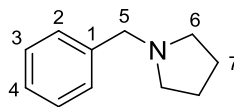
According to representative procedure 7.3.1, the product was purified by silica column chromatography (eluent; CH_2Cl_2 /hexanes, 2:1, $R_f = 0.39$, det: KMnO_4) and isolated as a colourless oil (372 mg, 70%). ^1H NMR: (CDCl_3 , 300 MHz) $\delta = 6.87$ (2H, d, $J = 9.00$ Hz, H_3), 6.56 (2H, d, $J = 9.00$ Hz, H_2), 3.78 (3H, s, H_7), 3.23-3.28 (4H, m, H_5), 1.99-2.03 (4H, m, H_6); ^{13}C NMR: (CDCl_3 , 75.4 MHz) $\delta = 150.4$ (C_4), 143.2 (C_1), 115.0 (C_2), 112.6 (C_3), 56.0 (C_7), 48.2 (C_5), 25.3 (C_6); HRMS(ESI-TOF): calcd. For $\text{C}_{11}\text{H}_{15}\text{NOH}^+$: 178.1232. Found: 178.1219 (MH^+). This is consistent with literature data.¹⁵

Methyl 4-(pyrrolidin-1-yl)benzoate **3.18**

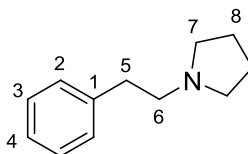
According to representative procedure 7.3.1, the product was purified by silica column chromatography (eluent; hexanes/EtOAc, 20:1, $R_f = 0.32$, det: KMnO_4) and isolated as a colourless oil (203 mg, 33%). m. p. 126-128 °C; IR: $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 2950, 2847, 1693, 1607, 1525, 1436, 1393; ^1H NMR: (CDCl_3 , 300 MHz) $\delta = 7.89$ (2H, d, $J = 9.00$ Hz, H_3), 6.50 (2H, d, $J = 9.00$ Hz, H_2), 3.85 (3H, s, H_8), 3.32-3.37 (4H, m, H_5), 2.00-2.05 (4H, m, H_6); ^{13}C NMR: (CDCl_3 , 75.4 MHz) $\delta = 167.6$ (C_7), 150.8 (C_1), 131.3 (C_3), 116.2 (C_2), 110.6 (C_4), 51.3 (C_8), 47.5 (C_5), 25.4 (C_6); HRMS(ESI-TOF): calcd. for $\text{C}_{12}\text{H}_{15}\text{NO}_2\text{H}^+$: 206.1181. Found: 206.1166 (MH^+), 228.0985 (MNa^+); CHN: *Anal. Calc.* for $\text{C}_{12}\text{H}_{15}\text{NO}_2$: C, 70.22%, H, 7.37%, N, 6.82%; Found: C, 70.05%, H, 7.26%, N, 6.62%.

1-(2,3-Dihydro-1H-inden-5-yl)pyrrolidine **3.19**

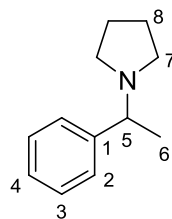
According to representative procedure 7.3.1, the product was purified by silica column chromatography (eluent; hexanes/EtOAc, 20:1, $R_f = 0.35$, det: KMnO_4) and isolated as a yellow oil (416 mg, 74%). ^1H NMR: (CDCl_3 , 300 MHz) $\delta = 7.12$ (1H, d, $J = 8.10$ Hz, H_5), 6.54 (1H, s, H_2), 6.40 (1H, d, $J = 8.10$ Hz, H_6), 3.28-3.32 (4H, m, H_7), 2.01-2.05 (4H, m, H_9 & H_{10}), 2.08 (2H, quin, $J = 7.50$ Hz, H_{11}), 2.00-2.05 (4H, m, H_8); ^{13}C NMR: (CDCl_3 , 75.4 MHz) $\delta = 147.2$ (C_1), 145.2 (C_3), 131.0 (C_4), 124.6 (C_5), 100.0 (C_2), 107.8 (C_6), 48.0 (C_7), 33.3 (C_9), 31.8 (C_{11}), 25.8 (C_{10}), 25.4 (C_8); HRMS(ESI-TOF): calcd. for $\text{C}_{13}\text{H}_{17}\text{NH}^+$: 188.1439. Found: 188.1425 (MH^+). This is consistent with literature data.²²

1-Benzylpyrrolidine **3.20**

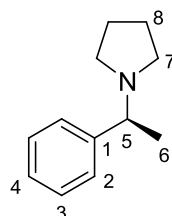
According to representative procedure 7.3.1, the product was purified by Kugelrohr distillation and isolated as a colourless oil (348 mg, 72%). ^1H NMR: (CDCl_3 , 300 MHz) δ = 7.14-7.29 (5H, m, arom.), 3.55 (2H, s, H_5), 2.42-2.47 (4H, m, H_6), 1.69-1.74 (4H, m, H_7); ^{13}C NMR: (CDCl_3 , 75.4 MHz) δ = 139.3 (C_1), 128.9 (C_3), 128.2 (C_2), 126.8 (C_4), 60.7 (C_5), 54.1 (C_6), 23.4 (C_7); HRMS(ESI-TOF): calcd. For $\text{C}_{11}\text{H}_{15}\text{NH}^+$: 162.1283. Found: 162.1272 (MH^+). This is consistent with literature data.¹⁵

1-Phenethylpyrrolidine **3.21**

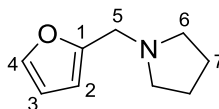
According to representative procedure 7.3.1, the product was purified by Kugelrohr distillation and isolated as a colourless oil (363 mg, 69%). ^1H NMR: (CDCl_3 , 300 MHz) δ = 7.18-7.33 (5H, m, arom.), 2.84-2.90 (2H, m, H_6), 2.69-2.75 (2H, m, H_5), 2.58-2.62 (4H, m, H_7), 1.81-1.85 (4H, m, H_8); ^{13}C NMR: (CDCl_3 , 75.4 MHz) δ = 140.5 (C_1), 128.6 (C_3), 128.3 (C_2), 125.9 (C_4), 58.3 (C_6), 54.2 (C_7), 35.8 (C_5), 23.4 (C_8); HRMS(ESI-TOF): calcd. For $\text{C}_{12}\text{H}_{17}\text{NH}^+$: 176.1439. Found: 176.1430 (MH^+). This is consistent with literature data.¹⁵

1-(Phenethyl)pyrrolidine **3.22**

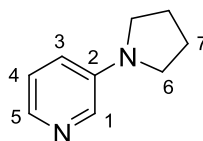
According to representative procedure 7.3.1, the product was purified by silica column chromatography (eluent; hexanes/EtOAc, 2:1, $R_f = 0.23$, det: KMnO_4) and isolated as a colourless oil (431 mg, 82%). ^1H NMR: (CDCl_3 , 300 MHz) $\delta = 7.14$ – 7.29 (5H, m, arom. H), 3.12 (1H, q, $J = 6.60$ Hz, H_5), 2.44–2.55 (2H, m, H_7), 2.26 – 2.33 (2H, m, H_7), 1.68 – 1.72 (4H, m, H_8), 1.34 (3H, d, $J = 6.60$ Hz, H_6); ^{13}C NMR: (CDCl_3 , 75.4 MHz) $\delta = 145.8$ (C_1), 128.3 (C_2), 127.3 (C_3), 126.9 (C_4), 66.1 (C_5), 53.1 (C_7), 23.5 (C_8), 23.3 (C_6); HRMS(ESI-TOF): calcd. for $\text{C}_{12}\text{H}_{17}\text{NH}^+$: 176.1439. Found: 176.1427 (MH^+). This is consistent with literature data.²³

(S)-1-(Phenethyl)pyrrolidine **3.23**

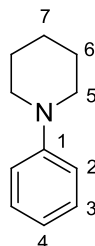
According to representative procedure 7.3.1, the product was purified by silica column chromatography (eluent; hexanes/EtOAc, 2:1, $R_f = 0.23$, det: KMnO_4) and isolated as a colourless oil (431 mg, 82%). $[\alpha]_D^{26}$: -66.5° (c 2.0, CHCl_3); ^1H NMR: (CDCl_3 , 300 MHz) $\delta = 7.14$ – 7.29 (5H, m, arom. H), 3.12 (1H, q, $J = 6.60$ Hz, H_5), 2.44–2.55 (2H, m, H_7), 2.26–2.33 (2H, m, H_7), 1.68–1.72 (4H, m, H_8), 1.34 (3H, d, $J = 6.60$ Hz, H_6); ^{13}C NMR: (CDCl_3 , 75.4 MHz) $\delta = 145.8$ (C_1), 128.3 (C_2), 127.3 (C_3), 126.9 (C_4), 66.1 (C_5), 53.1 (C_7), 23.5 (C_8), 23.3 (C_6); HRMS(ESI-TOF): calcd. for $\text{C}_{12}\text{H}_{17}\text{NH}^+$: 176.1439. Found: 176.1427 (MH^+). This is consistent with literature data.²⁴

1-(Furan-2-ylmethyl)pyrrolidine **3.24**

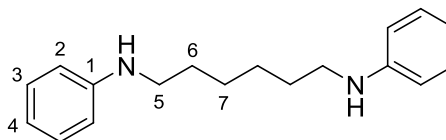
According to representative procedure 7.3.1, the product was purified by Kugelrohr distillation and isolated as a colourless oil (286 mg, 63%). ^1H NMR: (CDCl_3 , 300 MHz) δ = 7.35 (1H, dd, J = 1.80 0.60 Hz, H_4), 6.30 (1H, dd, J = 3.15 1.80 Hz, H_3), 6.18 (1H, dd, J = 3.15 0.60 Hz, H_2), 3.63 (2H, s, H_5), 2.52-2.56 (4H, m, H_6), 1.77-1.81 (4H, m, H_7); ^{13}C NMR: (CDCl_3 , 75.4 MHz) δ = 153.0 (C_1), 141.7 (C_4), 109.9 (C_3), 107.4 (C_2), 53.8 (C_6), 52.0 (C_5), 23.4 (C_7); HRMS(ESI-TOF): calcd. For $\text{C}_9\text{H}_{13}\text{NOH}^+$: 152.1075. Found: 152.1071 (MH^+). This is consistent with literature data.²⁵

3-(Pyrrolidin-1-yl)pyridine **3.26**

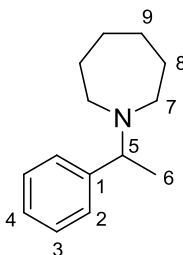
According to representative procedure 7.3.1, the product was purified by silica column chromatography (eluent; $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$, 1:1, R_f = 0.23, det: KMnO_4) and isolated as a yellow oil (256 mg, 58%). ^1H NMR: (CDCl_3 , 300 MHz) δ = 7.98 (1H, d, J = 3.00 Hz, H_1), 7.92 (1H, dd, J = 4.80 1.20 Hz, H_5), 7.08 (1H, ddd, J = 8.40 4.80 0.60 Hz, H_4), 6.80 (1H, ddd, J = 8.40 3.00 1.20 Hz, H_3), 3.27-3.32 (4H, m, H_6), 2.00-2.05 (4H, m, H_7); ^{13}C NMR: (CDCl_3 , 75.4 MHz) δ = 143.8 (C_2), 136.9 (C_5), 134.4 (C_1), 123.6 (C_4), 117.8 (C_3), 47.3 (C_6), 25.5 (C_7); HRMS(ESI-TOF): calcd. for $\text{C}_9\text{H}_{12}\text{N}_2\text{H}^+$: 149.1079. Found: 149.1076 (MH^+). This is consistent with literature data.²⁶

1-Phenylpiperidine **3.2**

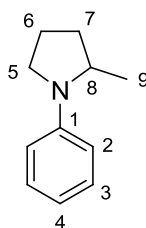
According to representative procedure 7.3.1, the product was purified by silica column chromatography (eluent; hexanes/EtOAc, 20:1, $R_f = 0.45$, det: KMnO_4) and isolated as a yellow oil (348 mg, 72%). ^1H NMR: (CDCl_3 , 300 MHz) $\delta = 7.29$ (2H, dd, $J = 9.00$ 7.20 Hz, H_3), 6.98 (2H, dd, $J = 9.00$ 1.05 Hz, H_2), 6.86 (1H, tt, $J = 7.20$ 1.05 Hz, H_4), 3.19 (4H, t, $J = 5.40$ Hz, H_5), 1.71-1.79 (4H, m, H_6), 1.57-1.65 (2H, m, H_7); ^{13}C NMR: (CDCl_3 , 75.4 MHz) $\delta = 152.2$ (C_1), 129.0 (C_3), 119.1 (C_2), 116.5 (C_4), 50.6 (C_5), 25.8 (C_6), 24.3 (C_7); HRMS(ESI-TOF): calcd. For $\text{C}_{11}\text{H}_{15}\text{NH}^+$: 162.1283 Found: 162.1277 (MH^+). This is consistent with literature data.²⁷

 N^1, N^6 -Diphenylhexanes-1,6-diamine **3.35**

According to representative procedure 7.3.1, the product was purified by silica column chromatography (eluent; CH_2Cl_2 , $R_f = 0.32$, det: KMnO_4) and isolated as a colourless solid (443 mg, 55%). m. p. 58-60 °C; IR : $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3393, 3051, 2925, 2854, 1602, 1505, 1478, 1460, 1429, 1322, 1261; ^1H NMR: (CDCl_3 , 300 MHz) $\delta = 7.18$ (2H, dd, $J = 8.55$ 7.35 Hz, H_3), 6.70 (1H, tt, $J = 7.35$ 0.90 Hz, H_4), 6.61 (2H, dd, $J = 8.55$ 0.90 Hz, H_2), 3.66 (2H, br s, NH), 3.12 (4H, t, $J = 7.05$ Hz, H_5), 1.60-1.69 (4H, m, H_6), 1.43-1.48 (4H, m, H_7); ^{13}C NMR: (CDCl_3 , 75.4 MHz) $\delta = 148.4$ (C_1), 129.2 (C_3), 117.1 (C_2), 112.6 (C_4), 43.8 (C_5), 29.5 (C_6), 26.9 (C_7); HRMS(ESI-TOF): calcd. For $\text{C}_{18}\text{H}_{24}\text{NH}^+$: 269.2018. Found: 269.2008 (MH^+); CHN: *Anal. Calc.* for $\text{C}_{18}\text{H}_{24}\text{N}_2$: C, 80.55%, H, 9.01%, N, 10.44%; Found: C, 79.40%, H, 8.88%, N, 10.25%.

1-(1-Phenylethyl)azepane **3.36**

According to representative procedure 7.3.1, the product was purified by silica column chromatography (eluent; hexanes/EtOAc, 10:1, $R_f = 0.19$, det: KMnO_4) and isolated as a yellow oil (396 mg, 65%). ^1H NMR: (CDCl_3 , 300 MHz) $\delta = 7.20\text{--}7.39$ (5H, arom.), 3.78 (1H, q, $J = 6.60$ Hz, H_5), 2.64 (4H, br s, H_7), 1.59 (8H, br s, H_8 & H_9), 1.37 (3H, d, H_6); ^{13}C NMR: (CDCl_3 , 75.4 MHz) $\delta = 144.9$ (C_1), 127.9 (C_2), 127.6 (C_3), 126.4 (C_4), 63.2 (C_5), 52.0 (C_7), 28.9 (C_8), 27.0 (C_9), 18.2 (C_6); HRMS(ESI-TOF): calcd. for $\text{C}_{14}\text{H}_{21}\text{NH}^+$: 204.1752. Found: 204.1735 (MH^+). This is consistent with literature data.²⁸

2-Methyl-1-phenylpyrrolidine **3.37**

According to representative procedure 7.3.1, the product was purified by Kugelrohr distillation and isolated as a yellow oil (314 mg, 65%). ^1H NMR: (CDCl_3 , 300 MHz) $\delta = 7.22$ (2H, dd, $J = 8.70, 7.20$ Hz, H_3), 6.64 (1H, tt, $J = 7.20, 0.90$ Hz, H_4), 6.59 (2H, dd, $J = 8.70, 0.90$ Hz, H_2), 3.84–3.93 (1H, m, H_8), 3.34–3.46 (1H, m, H_5), 3.09–3.21 (1H, m, H_5), 1.91–2.16 (3H, m, H_6 & H_7), 1.68–1.73 (1H, m, H_7), 1.18 (3H, d, $J = 6.30$ Hz, H_9); ^{13}C NMR: (CDCl_3 , 75.4 MHz) $\delta = 147.4$ (C_1), 129.3 (C_3), 115.3 (C_4), 111.9 (C_2), 53.7 (C_8), 48.3 (C_5), 33.2 (C_7), 23.4 (C_6), 19.5 (C_9); HRMS(ESI-TOF): calcd. for $\text{C}_{11}\text{H}_{15}\text{NH}^+$: 162.1283. Found: 162.1276 (MH^+). This is consistent with literature data.²⁹

7.4 Experimental procedures: Chapter 4

7.4.1 Representative Procedure for the Synthesis of Tertiary Amines from Secondary Amines under Microwave Conditions

To a microwave vial containing $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$ (45.9 mg, 0.075 mmol), DPEphos (80.8 mg, 0.15 mmol) was added the amine (3 mmol) and the alcohol (4.8 mmol, 1.6 eq.) before the vial was sealed. The vial was then purged with N_2 for 5 min before heating to 115 °C for 90 min. The crude product was then purified by silica column chromatography.

7.4.2 Representative Procedure for the Synthesis of 1,2-Amino Alcohols from Diols under Microwave Conditions

To a microwave vial containing (+/-)-1-phenyl-1,2-ethanediol (138 mg, 1 mmol), $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$ (15.3 mg, 0.025 mmol), DPEphos (0.05 mmol) was added the amine (2 mmol) before the vial was sealed. The vial was then purged with N_2 for 5 min before heating to 115 °C for 90 min. The crude product was then purified by silica column chromatography.

7.4.3 Representative Procedure for the Synthesis of Secondary Amines from Primary Amines under Microwave Conditions

To a microwave vial containing $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$ (15.3 mg, 0.025 mmol), DPEphos (0.05 mmol) were added the amine (1 mmol) and the alcohol (1.6 mmol) before the vial was sealed. The vial was then purged with N_2 for 5 min before heating to 125 °C for 90 min. The crude product was then purified by silica column chromatography.

7.4.4 Representative Procedure for the Synthesis of Cyclic Tertiary Amines from Primary Amines and Diols under Microwave Conditions

To a microwave vial containing $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$ (15.3 mg, 0.025 mmol), DPEphos (0.05 mmol) were added the amine (1 mmol) and the diol (1.6 mmol)

before the vial was sealed. The vial was then purged with N₂ for 5 min before heating to 135 °C for 90 min. The crude product was then purified by silica column chromatography.

7.4.5 Representative Procedure for the Synthesis of Cyclic Tertiary Amines from Primary Amines and Diols

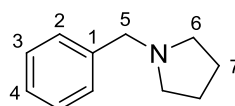
To a microwave vial containing *p*-toluenesulfonamide (171 mg, 1 mmol), [Ru(*p*-cymene)Cl₂]₂ (15.3 mg, 0.025 mmol), DPEphos (0.05 mmol) was added the alcohol (3 mmol) before the vial was sealed. The vial was then purged with N₂ for 5 min before heating to 165 °C for 180 min. The crude product was then purified by silica column chromatography.

7.4.6 Representative Procedure for the Synthesis of Secondary Amides from Primary Amides under Microwave Conditions

To a microwave vial containing benzamide (121 mg, 1 mmol), [Ru(*p*-cymene)Cl₂]₂ (15.3 mg, 0.025 mmol), DPEphos (0.05 mmol) was added the alcohol (3 mmol) before the vial was sealed. The vial was then purged with N₂ for 5 min before heating to 175 °C for 120 min. The crude product was then purified by silica column chromatography.

7.4.7 Ruthenium-Catalysed Synthesis of Tertiary Amines from Secondary Amines under Microwave Conditions

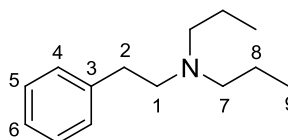
1-Benzylpyrrolidine **4.12**



According to representative procedure 7.4.1, the product was purified by silica column chromatography (eluent; CH₂Cl₂/MeOH, 95:5, R_f = 0.20, det: KMnO₄) and isolated as a brown oil (382 mg, 79%). ¹H NMR: (CDCl₃, 300 MHz) δ = 7.14-7.29

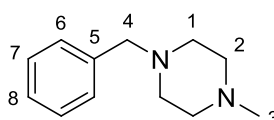
(5H, m, arom.), 3.55 (2H, s, H₅), 2.42-2.47 (4H, m, H₆), 1.69-1.74 (4H, m, H₇); ¹³C NMR: (CDCl₃, 75.4 MHz) δ = 139.3 (C₁), 128.9 (C₃), 128.2 (C₂), 126.8 (C₄), 60.7 (C₅), 54.1 (C₆), 23.4 (C₇); HRMS(ESI-TOF): calcd. For C₁₁H₁₅NH⁺: 162.1283. Found: 162.1272 (MH⁺). This is consistent with literature data.¹⁵

N-Phenethyl-*N*-propylpropan-1-amine **4.13**

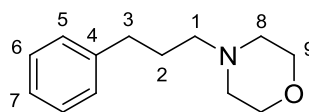


According to representative procedure 7.4.1, the product was purified by silica column chromatography (eluent; CH₂Cl₂/MeOH, 95:5, R_f = 0.19, det: KMnO₄) and isolated as a yellow oil (579 mg, 94%). ¹H NMR: (CDCl₃, 300 MHz) δ = 7.26-7.31 (2H, m, arom. H₅), 7.16-7.21 (3H, m, arom. H), 2.69-2.79 (4H, m, H₁ & H₂), 2.46-2.51 (4H, m, H₇), 1.44-1.57 (4H, m, H₈), 0.89 (6H, t, *J* = 7.50 Hz, H₉); ¹³C NMR: (CDCl₃, 75.4 MHz) δ = 141.1 (C₃), 128.9 (C₅), 128.4 (C₄), 126.0 (C₆), 56.3 (C₁ & C₇), 33.6 (C₂), 20.5 (C₈), 12.1 (C₉); HRMS(ESI-TOF): calcd. for C₁₄H₂₃NH⁺: 206.1909. Found: 206.1923 (MH⁺). This is consistent with literature data.³⁰

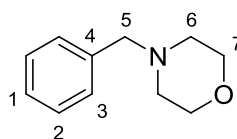
1-Benzyl-4-methylpiperazine **4.14**



According to representative procedure 7.4.1, the product was purified by silica column chromatography (eluent; CH₂Cl₂/MeOH, 9:1, R_f = 0.19, det: KMnO₄) and isolated as a yellow oil (451 mg, 79%). ¹H NMR: (CDCl₃, 300 MHz) δ = 7.21-7.32 (5H, m, arom. H), 3.51 (2H, s, H₄), 2.47 (8H, br s, H₁ & H₂), 2.29 (3H, s, H₃); ¹³C NMR: (CDCl₃, 75.4 MHz) δ = 138.3 (C₅), 129.3 (C₆), 128.3 (C₇), 127.1 (C₈), 63.2 (C₄), 55.3 (C₂), 53.2 (C₁), 46.2 (C₃); HRMS(ESI-TOF): calcd. for C₁₂H₁₈N₂H⁺: 191.1548. Found: 191.1543 (MH⁺). This is consistent with literature data.³¹

4-(3-Phenylpropyl)morpholine **4.15**

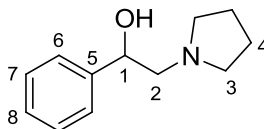
According to representative procedure 7.4.1, the product was purified by silica column chromatography (eluent; Et₂O/petroleum ether b. p. 40-60 °C, 3:1, R_f = 0.20, det: KMnO₄) and isolated as a brown oil (511 mg, 83%). ¹H NMR: (CDCl₃, 300 MHz) δ = 7.26-7.31 (2H, m, arom. H), 7.16-7.20 (3H, m, arom. H), 3.73 (4H, app t, *J* = 4.65 Hz, H₉), 2.65 (2H, t, *J* = 7.65 Hz, H₃), 2.45 (4H, m, H₈), 2.38 (2H, t, *J* = 7.65 Hz, H₁), 1.78-1.89 (2H, m, H₂); ¹³C NMR: (CDCl₃, 75.4 MHz) δ = 142.2 (C₄), 128.5 (C₆), 128.4 (C₅), 125.9 (C₇), 67.1 (C₉), 58.5 (C₈), 53.4 (C₁), 33.7 (C₃), 28.4 (C₂); HRMS(ESI-TOF): calcd. for C₁₃H₁₉NOH⁺: 206.1545. Found: 206.1548 (MH⁺). This is consistent with literature data.³¹

4-Benzylmorpholine **4.8**

According to representative procedure 7.4.1, the product was purified by silica column chromatography (eluent; petroleum ether b. p. 40-60 °C/EtOAc, 3:1, R_f = 0.19, det: KMnO₄) and isolated as a brown oil (431 mg, 81%). ¹H NMR: (CDCl₃, 300 MHz) δ = 7.20-7.27 (5H, m, arom. H), 3.66 (4H, t, *J* = 4.65 Hz, H₇), 3.45 (2H, s, H₅), 2.39 (4H, t, *J* = 4.50 Hz, H₆); ¹³C NMR: (CDCl₃, 75.4 MHz) δ = 137.7 (C₁), 129.3 (C₃), 128.3 (C₂), 127.2 (C₄), 67.0 (C₇), 63.5 (C₅), 53.6 (C₆); HRMS(ESI-TOF): calcd. for C₁₁H₁₆NOH⁺: 178.1232. Found: 178.1229 (MH⁺). This is consistent with literature data.³¹

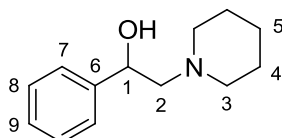
7.4.8 Ruthenium-Catalysed Synthesis of 1,2-Amino Alcohols from Diols under Microwave Conditions

1-Phenyl-2-(pyrrolidin-1-yl)ethanol **4.16**

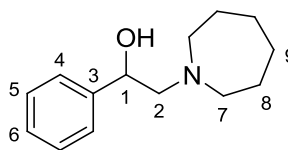


According to representative procedure 7.4.2, the product was purified by silica column chromatography (eluent; Et₂O/CH₂Cl₂, 2:1, R_f = 0.16, det: KMnO₄) and isolated as a colourless solid (143 mg, 75%). ¹H NMR: (CDCl₃, 300 MHz) δ = 7.24-7.41 (5H, m, arom. H), 4.74 (1H, dd, *J* = 10.80 3.30 Hz, H₁), 3.89 (1H, br s, OH), 2.78-2.85 (3H, m, H₂ & H₃), 2.50-2.63 (3H, m, H₂ & H₃), 1.81-1.85 (4H, m, H₄); ¹³C NMR: (CDCl₃, 75.4 MHz) δ = 142.5 (C₅), 128.4 (C₇), 127.5 (C₈), 126.0 (C₆), 70.8 (C₁), 64.2 (C₂), 54.0 (C₃), 23.8 (C₄); HRMS(ESI-TOF): calcd. for C₁₂H₁₇NOH⁺: 192.1388. Found: 192.1399 (MH⁺). This is consistent with literature data.³²

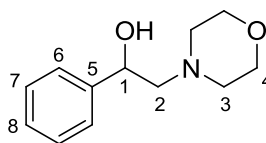
1-Phenyl-2-(piperidin-1-yl)ethanol **4.17**



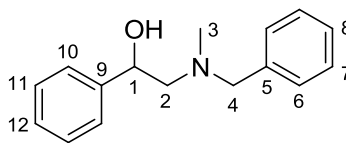
According to representative procedure 7.4.2, the product was purified by silica column chromatography (eluent; Et₂O/CH₂Cl₂, 2:1, R_f = 0.23, det: KMnO₄) and isolated as a colourless solid (162 mg, 79%). ¹H NMR: (CDCl₃, 300 MHz) δ = 7.23-7.40 (5H, m, arom. H), 4.73 (1H, dd, *J* = 10.50 3.90 Hz, H₁), 4.19 (1H, br s, OH), 2.69-2.71 (2H, m, H₂), 2.36-2.53 (4H, m, H₃), 1.59-1.66 (4H, m, H₄), 1.46-1.51 (2H, m, H₅); ¹³C NMR: (CDCl₃, 75.4 MHz) δ = 142.6 (C₆), 128.4 (C₈), 127.5 (C₉), 126.0 (C₇), 68.8 (C₁), 67.1 (C₂), 54.6 (C₃), 26.3 (C₄), 24.4 (C₅); HRMS(ESI-TOF): calcd. for C₁₃H₁₉NOH⁺: 206.1545. Found: 206.1544 (MH⁺). This is consistent with literature data.³²

2-(Azepan-1-yl)-1-phenylethanol **4.18**

According to representative procedure 7.4.2, the product was purified by silica column chromatography (eluent; Et₂O/CH₂Cl₂, 3:2, R_f = 0.24, det: KMnO₄) and isolated as a yellow oil (173 mg, 65%). ¹H NMR: (CDCl₃, 300 MHz) δ = 7.23-7.42 (5H, m, arom. H), 4.70 (1H, dd, *J* = 10.80 3.30 Hz, H₁), 3.59 (1H, br s, OH), 2.88-2.96 (2H, m, H₇), 2.73-2.84 (3H, m, H₂ & H₇), 2.51 (1H, dd, *J* = 12.60 10.80 Hz, H₂), 1.63-1.77 (8H, m, H₈ & H₉); ¹³C NMR: (CDCl₃, 75.4 MHz) δ = 142.5 (C₃), 128.4 (C₅), 127.5 (C₆), 126.0 (C₄), 69.4 (C₁), 66.3 (C₂), 55.7 (C₇), 28.3 (C₈), 27.1 (C₉); HRMS(ESI-TOF): calcd. for C₁₄H₂₁NOH⁺: 220.1701. Found: 220.1686 (MH⁺). This is consistent with literature data.³³

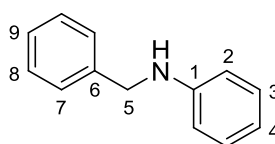
2-Morpholino-1-phenylethanol **4.19**

According to representative procedure 7.4.2, the product was purified by silica column chromatography (eluent; EtOAc/EtOH, 30:1, R_f = 0.26, det: KMnO₄) and isolated as a colourless solid (187 mg, 90%). ¹H NMR: (CDCl₃, 300 MHz) δ = 7.28-7.39 (5H, m, arom. H), 4.80 (1H, dd, *J* = 10.20 4.20 Hz, H₁), 3.76-3.80 (4H, m, H₄), 2.75-2.82 (2H, m, H₂), 2.47-2.57 (4H, m, H₃); ¹³C NMR: (CDCl₃, 75.4 MHz) δ = 142.0 (C₅), 128.5 (C₇), 127.7 (C₈), 126.0 (C₆), 68.7 (C₁), 67.2 (C₄), 66.8 (C₂), 53.6 (C₃); HRMS(ESI-TOF): calcd. for C₁₂H₁₇NO₂H⁺: 208.1338. Found: 208.1338 (MH⁺). This is consistent with literature data.³²

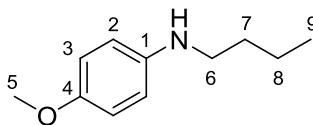
2-(Benzyl(methyl)amino)-1-phenylethanol **4.20**

According to representative procedure 7.4.2, the product was purified by silica column chromatography (eluent; hexane/Et₂O, 3:2, R_f = 0.25, det: KMnO₄) and isolated as a brown oil (147 mg, 61%). ¹H NMR: (CDCl₃, 300 MHz) δ = 7.26-7.38 (10H, m, arom. H), 4.77 (1H, dd, J = 10.20 3.90 Hz, H₁), 3.77 (1H, d, J = 13.20 Hz, H₄), 3.57 (1H, d, J = 13.20 Hz, H₄), 2.63 (1H, dd, J = 12.30 10.30 Hz, H₂), 2.55 (1H, dd, J = 12.60 10.30 Hz, H₂), 2.35 (3H, s, H₃); ¹³C NMR: (CDCl₃, 75.4 MHz) δ = 142.3 (C₉), 138.2 (C₅), 129.2 (C₁₁), 128.5 (C₆), 128.4 (C₇), 127.6 (C₈), 127.5 (C₁₂), 126.0 (C₁₀), 69.5 (C₁), 65.6 (C₂), 62.5 (C₄), 41.9 (C₃); HRMS(ESI-TOF): calcd. for C₁₆H₁₉NOH⁺: 242.1545. Found: 242.1557 (MH⁺). This is consistent with literature data.³⁴

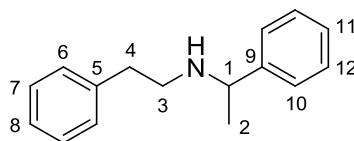
7.4.9 Ruthenium-Catalysed Synthesis of Secondary Amines from Primary Amines under Microwave Conditions

N-Benzylaniline **4.21**

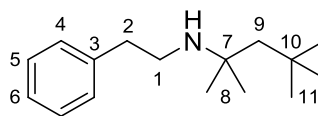
According to representative procedure 7.4.3, the product was purified by silica column chromatography (eluent; petroleum ether b. p. 40-60 °C/Et₂O, 20:1, R_f = 0.30, det: KMnO₄) and isolated as a brown oil (112 mg, 61%). ¹H NMR: (CDCl₃, 300 MHz) δ = 7.27-7.40 (5H, m, arom. H), 7.15-7.21 (2H, m, H₃), 6.76 (1H, t, J = 7.50 Hz, H₄), 6.69 (2H, d, J = 7.50 Hz, H₂), 4.88 (1H, br s, NH), 4.34 (2H, s, H₅); ¹³C NMR: (CDCl₃, 75.4 MHz) δ = 148.2 (C₁), 139.5 (C₆), 129.4 (C₃), 128.8 (C₈), 127.7 (C₇), 127.4 (C₉), 117.8 (C₄), 113.1 (C₂), 48.5 (C₅); HRMS(ESI-TOF): calcd. for C₁₃H₁₃NH⁺: 184.1126. Found: 184.1104 (MH⁺). This is consistent with literature data.³¹

***N*-Butyl-4-methoxyaniline 4.22**

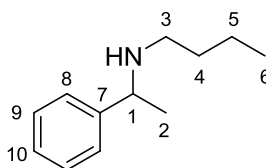
According to representative procedure 7.4.3, the product was purified by silica column chromatography (eluent; petroleum ether b. p. 40-60 °C/Et₂O, 9:1, *R_f* = 0.17, det: KMnO₄) and isolated as a yellow oil (131 mg, 73%). ¹H NMR: (CDCl₃, 300 MHz) δ = 6.76-6.81 (2H, m, H₃), 6.57-6.63 (2H, m, H₂), 3.75 (3H, s, H₅), 3.07 (2H, t, *J* = 7.20 Hz, H₆), 1.55-1.65 (2H, m, H₇), 1.36-1.49 (2H, m, H₈), 0.95 (3H, t, *J* = 7.20 Hz, H₉); ¹³C NMR: (CDCl₃, 75.4 MHz) δ = 152.1 (C₄), 143.0 (C₁), 115.0 (C₃), 114.2 (C₂), 56.0 (C₅), 44.9 (C₆), 31.9 (C₇), 20.5 (C₈), 14.1 (C₉); HRMS(ESI-TOF): calcd. for C₁₁H₁₇NOH⁺ : 180.1388. Found : 180.1369 (MH⁺). This is consistent with literature data.³⁵

***N*-Phenethyl-1-phenethanamine 4.23**

According to representative procedure 7.4.3, the product was purified by silica column chromatography (eluent; CH₂Cl₂/Et₂O, 4:1, *R_f* = 0.24, det: KMnO₄) and isolated as a brown oil (212 mg, 94%). ¹H NMR: (CDCl₃, 300 MHz) δ = 7.15-7.34 (10H, m, arom. H), 3.79 (1H, q, *J* = 6.60 Hz, H₁), 2.68-2.83 (4H, m, H₃ & H₄), 1.35 (3H, d, *J* = 6.60 Hz, H₂); ¹³C NMR: (CDCl₃, 75.4 MHz) δ = 145.7 (C₉), 140.2 (C₅), 128.8 (C₁₂), 128.5 (C₇), 128.5 (C₁₀), 127.0 (C₁₁), 126.7 (C₆), 126.2 (C₈), 58.3 (C₁), 49.0 (C₃), 36.5 (C₄), 24.4 (C₂); HRMS(ESI-TOF): calcd. for C₁₆H₁₉NH⁺: 226.1596. Found: 226.1569 (MH⁺). This is consistent with literature data.³¹

2,4,4-Trimethyl-*N*-phenethylpentan-2-amine **4.24**

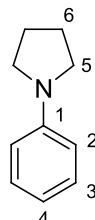
According to representative procedure 7.4.3, the product was purified by silica column chromatography (eluent; CH₂Cl₂/MeOH, 92:8, *R_f* = 0.31, det: KMnO₄) and isolated as a brown oil (191 mg, 82%). ¹H NMR: (CDCl₃, 300 MHz) δ = 7.20-7.32 (5H, m, arom. H), 2.84 (4H, app. br s, H₁ & H₂), 1.44 (2H, s, H₉), 1.16 (6H, s, H₈), 0.95 (9H, s, H₁₁); ¹³C NMR: (CDCl₃, 75.4 MHz) δ = 140.5 (C₃), 128.9 (C₅), 128.5 (C₄), 126.2 (C₆), 54.4 (C₇), 53.1 (C₉), 43.8 (C₁), 37.3 (C₂), 31.8 (C₁₁), 31.7 (C₁₀), 29.0 (C₈); HRMS(ESI-TOF): calcd. for C₁₆H₂₇NH⁺: 234.2222. Found: 234.2229 (MH⁺). This is consistent with literature data.³⁶

N-(1-Phenethyl)butan-1-amine **4.25**

According to representative procedure 7.4.3, the product was purified by silica column chromatography (eluent; petroleum ether b. p. 40-60 °C/Et₂O, 1:1, *R_f* = 0.25, det: KMnO₄) and isolated as a yellow oil (142 mg, 80%). ¹H NMR: (CDCl₃, 300 MHz) δ = 7.21-7.36 (5H, m, arom. H), 3.77 (1H, q, *J* = 6.60 Hz, H₁), 2.38-2.55 (2H, m, H₃), 1.78 (1H, br s, NH), 1.41-1.52 (2H, m, H₄), 1.38 (3H, d, *J* = 6.60 Hz, H₂), 1.23-1.34 (2H, m, H₅), 0.87 (3H, t, *J* = 7.20 Hz, H₆); ¹³C NMR: (CDCl₃, 75.4 MHz) δ = 146.0 (C₇), 128.5 (C₉), 126.9 (C₁₀), 126.7 (C₈), 58.5 (C₁), 47.7 (C₃), 32.5 (C₄), 24.5 (C₂), 20.6 (C₅), 14.1 (C₆); HRMS(ESI-TOF): calcd. for C₁₂H₁₉NH⁺: 178.1596. Found: 178.1592 (MH⁺). This is consistent with literature data.³⁷

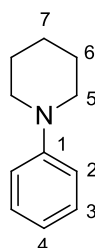
7.4.10 Ruthenium-Catalysed Synthesis of Cyclic Tertiary Amines from Primary Amines and Diols under Microwave Conditions

1-Phenylpyrrolidine **4.26**



According to representative procedure 7.4.4, the product was purified by silica column chromatography (eluent; hexanes/EtOAc, 20:1, R_f = 0.52, det: KMnO_4) and isolated as a yellow oil (130 mg, 88%). ^1H NMR: (CDCl_3 , 300 MHz) δ = 7.23 (2H, dd, J = 8.70 7.20 Hz, H_3), 6.67 (1H, t, J = 7.20 Hz, H_4), 6.59 (2H, d, J = 8.10, H_2), 3.27-3.32 (4H, m, H_5), 1.97-2.05 (4H, m, H_6); ^{13}C NMR: (CDCl_3 , 75.4 MHz) δ = 148.1 (C_1), 129.3 (C_3), 115.5 (C_2), 111.8 (C_4), 47.7 (C_5), 25.6 (C_6); HRMS(ESI-TOF): calcd. For $\text{C}_{10}\text{H}_{13}\text{NH}^+$: 148.1126. Found: 148.1106 (MH^+). This is consistent with literature data.³¹

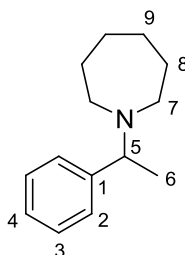
1-Phenylpiperidine **4.27**



According to representative procedure 7.4.4, the product was purified by silica column chromatography (eluent; hexanes/EtOAc, 20:1, R_f = 0.45, det: KMnO_4) and isolated as a yellow oil (131 mg, 81%). ^1H NMR: (CDCl_3 , 300 MHz) δ = 7.23-7.28 (2H, m, H_3), 6.96-6.98 (2H, br s, H_2), 6.82-6.86 (1H, m, H_4), 3.16 (4H, t, J = 5.40 Hz, H_5), 1.73 (4H, br s, H_6), 1.58-1.62 (2H, m, H_7); ^{13}C NMR: (CDCl_3 , 75.4 MHz) δ = 152.4 (C_1), 129.1 (C_3), 119.3 (C_2), 116.7 (C_4), 50.8 (C_5), 26.0 (C_6), 24.5 (C_7);

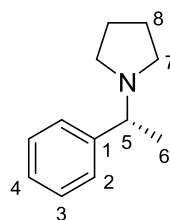
HRMS(ESI-TOF): calcd. For $C_{11}H_{15}NH^+$: 162.1283 Found: 162.1260 (MH^+). This is consistent with literature data.³¹

1-(1-Phenylethyl)azepane **4.28**



According to representative procedure 7.4.4, the product was purified by silica column chromatography (eluent; hexanes/EtOAc, 10:1, R_f = 0.19, det: $KMnO_4$) and isolated as a yellow oil (157 mg, 77%). 1H NMR: ($CDCl_3$, 300 MHz) δ = 7.19-7.39 (5H, arom.), 3.77 (1H, q, J = 6.60 Hz, H_5), 2.63 (4H, br s, H_7), 1.58 (8H, br s, H_8 & H_9), 1.36 (3H, d, H_6); ^{13}C NMR: ($CDCl_3$, 75.4 MHz) δ = 145.1 (C_1), 128.1 (C_2), 127.7 (C_3), 126.6 (C_4), 63.4 (C_5), 52.2 (C_7), 29.1 (C_8), 27.2 (C_9), 18.4 (C_6); HRMS(ESI-TOF): calcd. for $C_{14}H_{21}NH^+$: 204.1752. Found: 204.1743 (MH^+). This is consistent with literature data.³¹

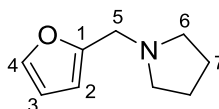
(*R*)-1-(Phenethyl)pyrrolidine **4.29**



According to representative procedure 7.4.4, the product was purified by silica column chromatography (eluent; hexanes/EtOAc, 2:1, R_f = 0.23, det: $KMnO_4$) and isolated as a colourless oil (144 mg, 82%). $[\alpha]_D^{26}$: +62.1° (c 2.1, $CHCl_3$); 1H NMR: ($CDCl_3$, 300 MHz) δ = 7.12-7.29 (5H, m, arom. H), 3.12 (1H, q, J = 6.60 Hz, H_5), 2.46-2.51 (2H, m, H_7), 2.27-2.33 (2H, m, H_7), 1.67-1.72 (4H, m, H_8), 1.34 (3H, d, J = 6.60 Hz, H_6); ^{13}C NMR: ($CDCl_3$, 75.4 MHz) δ = 145.9 (C_1), 128.4 (C_2), 127.3 (C_3), 126.9 (C_4), 66.1 (C_5), 53.1 (C_7), 23.5 (C_8), 23.3 (C_6); HRMS(ESI-TOF): calcd. for

$\text{C}_{12}\text{H}_{17}\text{NH}^+$: 176.1439. Found: 176.1422 (MH^+). This is consistent with literature data.³⁸

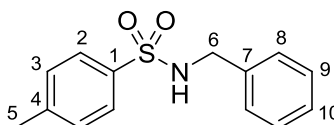
1-(Furan-2-ylmethyl)pyrrolidine **4.30**



According to representative procedure 7.4.4, the product was purified by Kugelrohr distillation and isolated as a colourless oil (82 mg, 54%). ^1H NMR: (CDCl_3 , 300 MHz) δ = 7.35 (1H, dd, J = 1.80 0.60 Hz, H_4), 6.30 (1H, dd, J = 3.15 1.80 Hz, H_3), 6.18 (1H, dd, J = 3.15 0.60 Hz, H_2), 3.63 (2H, s, H_5), 2.52-2.56 (4H, m, H_6), 1.77-1.81 (4H, m, H_7); ^{13}C NMR: (CDCl_3 , 75.4 MHz) δ = 153.1 (C_1), 141.9 (C_4), 110.1 (C_3), 107.6 (C_2), 54.0 (C_6), 52.2 (C_5), 23.6 (C_7); HRMS(ESI-TOF): calcd. For $\text{C}_9\text{H}_{13}\text{NOH}^+$: 152.1075. Found: 152.1071 (MH^+). This is consistent with literature data.³¹

7.4.11 Ruthenium-Catalysed Alkylation of Sulfonamides under Microwave Conditions

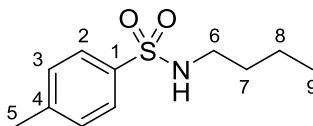
N-Benzyl-4-methylbenzenesulfonamide **4.31**



According to representative procedure 7.4.5, the product was purified by silica column chromatography (eluent; CH_2Cl_2 , R_f = 0.27, det: KMnO_4) and isolated as an off-white solid (238 mg, 91%). ^1H NMR: (CDCl_3 , 300 MHz) δ = 7.77 (2H, d, J = 8.40 Hz, H_2), 7.26-7.33 (5H, m, arom. H), 7.18-7.23 (2H, m, H_8), 4.59 (1H, br t, J = 5.70 Hz, NH), 4.13 (2H, d, J = 6.00 Hz, H_6), 2.44 (3H, s, H_5); ^{13}C NMR: (CDCl_3 , 75.4 MHz) δ = 143.6 (C_1), 137.0 (C_7), 136.4 (C_4), 129.9 (C_3), 128.8 (C_9), 128.0 (C_{10}), 128.0 (C_2), 127.3 (C_8), 47.4 (C_6), 21.7 (C_5); HRMS(ESI-TOF): calcd. for

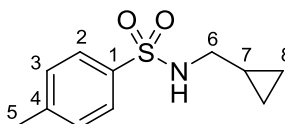
$\text{C}_{14}\text{H}_{15}\text{NO}_2\text{SH}^+$: 262.0912. Found: 262.0903 (MH^+), 284.0723 (MNa^+). This is consistent with literature data.³¹

N-Butyl-4-methylbenzenesulfonamide **4.32**

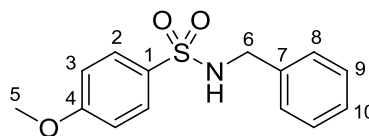


According to representative procedure 7.4.5, the product was purified by silica column chromatography (eluent; CH_2Cl_2 , $R_f = 0.25$, det: KMnO_4) and isolated as a colourless solid (218 mg, 96%). ^1H NMR: (CDCl_3 , 300 MHz) $\delta = 7.74$ (2H, d, $J = 8.10$ Hz, H_2), 7.31 (2H, d, $J = 8.10$ Hz, H_3), 4.30 (1H, br s, NH), 2.93 (2H, t, $J = 6.90$ Hz, H_6), 2.43 (3H, s, H_5), 1.39-1.49 (2H, m, H_7), 1.23-1.35 (2H, m, H_8), 0.85 (3H, t, $J = 7.20$ Hz, H_9); ^{13}C NMR: (CDCl_3 , 75.4 MHz) $\delta = 143.4$ (C_4), 137.0 (C_1), 129.8 (C_3), 127.2 (C_2), 43.0 (C_6), 31.6 (C_7), 21.6 (C_5), 19.8 (C_8), 13.6 (C_9); HRMS(ESI-TOF): calcd. for $\text{C}_{11}\text{H}_{17}\text{NO}_2\text{SH}^+$: 228.1058. Found: 228.1051 (MH^+), 250.0871 (MNa^+). This is consistent with literature data.³⁹

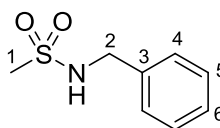
N-(Cyclopropylmethyl)-4-methylbenzenesulfonamide **4.33**



According to representative procedure 7.4.5, the product was purified by silica column chromatography (eluent; CH_2Cl_2 , $R_f = 0.22$, det: KMnO_4) and isolated as a colourless solid (167 mg, 74%). ^1H NMR: (CDCl_3 , 300 MHz) $\delta = 7.75$ (2H, d, $J = 8.10$ Hz, H_2), 7.30 (2H, d, $J = 8.10$ Hz, H_3), 4.45 (1H, br t, $J = 5.40$ Hz, NH), 2.81 (2H, dd, $J = 7.20$ 6.00 Hz, H_6), 2.43 (3H, s, H_5), 0.81-0.94 (1H, m, H_7), 0.43-0.49 (2H, m, H_8), 0.06-0.11 (2H, m, H_8); ^{13}C NMR: (CDCl_3 , 75.4 MHz) $\delta = 143.4$ (C_4), 137.2 (C_1), 129.8 (C_3), 127.2 (C_2), 48.4 (C_6), 21.6 (C_5), 10.8 (C_7), 3.6 (C_8); HRMS(ESI-TOF): calcd. for $\text{C}_{11}\text{H}_{15}\text{NO}_2\text{SH}^+$: 226.0902. Found: 226.0902 (MH^+), 248.0724 (MNa^+). This is consistent with literature data.³¹

N-Benzyl-4-methoxybenzenesulfonamide **4.34**

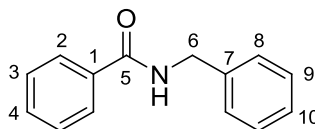
According to representative procedure 7.4.5, the product was purified by silica column chromatography (eluent; CH₂Cl₂/MeOH, 99:1, *R_f* = 0.43, det: KMnO₄) and isolated as a colourless solid (252 mg, 91%). ¹H NMR: (CDCl₃, 300 MHz) δ = 7.82 (2H, d, *J* = 8.85 Hz, H₂), 7.27-7.29 (3H, m, arom. H), 7.18-7.21 (2H, m, H₈), 6.98 (2H, d, *J* = 8.85 Hz, H₃), 4.53 (1H, br t, *J* = 6.00 Hz, NH), 4.13 (2H, d, *J* = 6.30 Hz, H₆), 3.88 (3H, s, H₅); ¹³C NMR: (CDCl₃, 75.4 MHz) δ = 163.1 (C₄), 136.5 (C₇), 131.6 (C₁), 129.4 (C₉), 128.8 (C₈), 128.0 (C₂ & C₁₀), 114.4 (C₃), 55.8 (C₅), 47.4 (C₆); HRMS(ESI-TOF): calcd. for C₁₄H₁₅NO₃Na⁺: 300.0670. Found: 300.0636 (MNa⁺). This is consistent with literature data.³¹

N-Benzylmethanesulfonamide **4.35**

According to representative procedure 7.4.5, the product was purified by silica column chromatography (eluent; CH₂Cl₂/MeOH, 98:2, *R_f* = 0.37, det: KMnO₄) and isolated as a yellow solid (159 mg, 86%). ¹H NMR: (CDCl₃, 300 MHz) δ = 7.32-7.41 (5H, m, arom. H), 4.59 (1H, br s, NH), 4.33 (2H, d, *J* = 6.00 Hz, H₂), 2.88 (3H, s, H₁); ¹³C NMR: (CDCl₃, 75.4 MHz) δ = 136.8 (C₃), 129.0 (C₅), 128.2 (C₆), 128.0 (C₄), 47.3 (C₂), 41.2 (C₁); HRMS(ESI-TOF): calcd. for C₈H₁₁NO₂SN⁺: 208.0408. Found: 208.0404 (MNa⁺). This is consistent with literature data.³¹

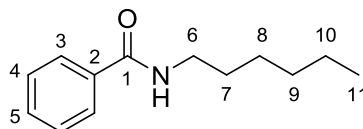
7.4.12 Ruthenium-Catalysed Synthesis of Secondary Amides from Primary Amides under Microwave Conditions

N-Benzylbenzamide **4.36**

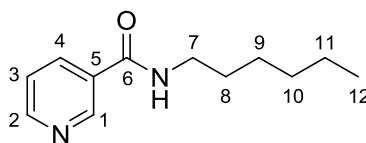


According to representative procedure 7.4.6, the product was purified by silica column chromatography (eluent; petroleum ether b. p. 40-60 °C/Et₂O, 1:1, *R_f* = 0.22, det: KMnO₄) and isolated as a colourless solid (139 mg, 66%). ¹H NMR: (CDCl₃, 300 MHz) δ = 7.78-7.81 (2H, m, H₂), 7.29-7.53 (8H, arom. H), 6.39 (1H, br s, NH), 4.66 (2H, d, *J* = 5.40 Hz, H₆); ¹³C NMR: (CDCl₃, 75.4 MHz) δ = 167.5 (C₅), 138.3 (C₇), 134.5 (C₁), 131.7 (C₄), 128.9 (C₃), 128.7 (C₉), 128.0 (C₂), 127.7 (C₁₀), 127.1 (C₈), 44.3 (C₆); HRMS(ESI-TOF): calcd. for C₁₄H₁₃NOH⁺: 212.1075. Found: 212.1070 (MH⁺), 234.0885 (MNa⁺). This is consistent with literature data.⁴⁰

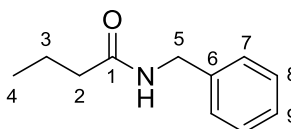
N-Hexylbenzamide **4.37**



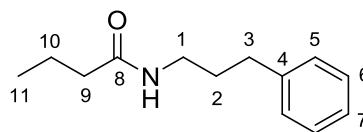
According to representative procedure 7.4.6, the product was purified by silica column chromatography (eluent; petroleum ether b. p. 40-60 °C/Et₂O, 1:1, *R_f* = 0.30, det: KMnO₄) and isolated as a colourless solid (148 mg, 72%). ¹H NMR: (CDCl₃, 300 MHz) δ = 7.74-7.77 (2H, m, H₃), 7.40-7.52 (3H, m, arom. H), 6.10 (1H, br s, NH), 3.42-3.49 (2H, m, H₆), 1.57-1.67 (2H, m, H₇), 1.28-1.44 (6H, m, H₈, H₉ & H₁₀), 0.90 (3H, t, *J* = 6.90 Hz, H₁₁); ¹³C NMR: (CDCl₃, 75.4 MHz) δ = 167.6 (C₁), 135.0 (C₂), 131.4 (C₅), 128.6 (C₄), 127.0 (C₃), 40.2 (C₆), 31.6 (C₇), 29.8 (C₈), 26.8 (C₉), 22.7 (C₁₀), 14.1 (C₁₁); HRMS(ESI-TOF): calcd. for C₁₃H₁₉NOH⁺: 206.1545. Found: 206.1535 (MH⁺), 228.1349 (MNa⁺). This is consistent with literature data.⁴¹

N-Hexylnicotinamide 4.38

According to representative procedure 7.4.6, the product was purified by silica column chromatography (eluent; Et₂O/MeOH, 50:1, R_f = 0.18, det: KMnO₄) and isolated as a yellow oil (111 mg, 54%). ¹H NMR: (CDCl₃, 300 MHz) δ = 9.04 (1H, d, *J* = 1.80 Hz, H₁), 8.71 (1H, dd, *J* = 5.10 1.50 Hz, H₂), 8.18 (1H, app. dt, *J* = 7.80 1.95 Hz, H₄), 7.42 (1H, ddd, 7.80 4.80 0.60 Hz, H₃), 6.41 (1H, br s, NH), 3.47 (1H, dt, 7.20 6.00 Hz, H₇), 1.59-1.68 (2H, m, H₈), 1.29-1.44 (6H, m, H₉, H₁₀ & H₁₁), 0.87-0.92 (3H, m, H₁₂); ¹³C NMR: (CDCl₃, 75.4 MHz) δ = 165.7 (C₆), 152.0 (C₁), 147.9 (C₂), 135.3 (C₄), 130.7 (C₅), 123.6 (C₃), 40.4 (C₇), 31.6 (C₈), 29.6 (C₉), 26.7 (C₁₀), 22.6 (C₁₁), 14.1 (C₁₂); HRMS(ESI-TOF): calcd. for C₁₂H₁₈N₂OH⁺: 207.1497. Found: 207.1511 (MH⁺), 229.1323 (MNa⁺). This is consistent with literature data.⁴²

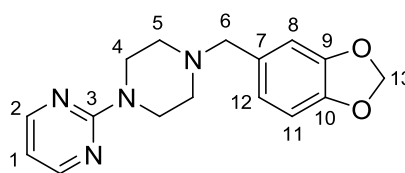
N-Benzylbutyramide 4.39

According to representative procedure 7.4.6, the product was purified by silica column chromatography (eluent; hexanes/EtOAc, 20:1, R_f = 0.32, det: KMnO₄) and isolated as a colourless solid (131 mg, 74%). ¹H NMR: (CDCl₃, 300 MHz) δ = 7.26-7.36 (5H, m, arom. H), 5.70 (1H, br s, NH), 4.45 (2H, d, *J* = 5.70 Hz, H₅), 2.20 (2H, t, *J* = 7.50 Hz, H₂), 1.64-1.76 (2H, m, H₃), 0.96 (3H, t, *J* = 7.50 Hz, H₄); ¹³C NMR: (CDCl₃, 75.4 MHz) δ = 172.9 (C₁), 138.6 (C₆), 128.8 (C₈), 127.9 (C₇), 127.6 (C₉), 43.7 (C₅), 38.8 (C₂), 19.3 (C₃), 13.9 (C₄); HRMS(ESI-TOF): calcd. for C₁₁H₁₅NOH⁺: 178.1232. Found: 178.1218 (MH⁺), 200.1037 (MNa⁺). This is consistent with literature data.⁴³

***N*-(3-Phenylpropyl)butyramide 4.40**

According to representative procedure 7.4.6, the product was purified by silica column chromatography (eluent; Et₂O/petroleum ether b. p. 40-60 °C, 3:1, *R_f* = 0.24, det: KMnO₄) and isolated as a yellow oil (162 mg, 79%). IR: $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3291, 2962, 2934, 1638, 1546, 1454, 744, 697; ¹H NMR: (CDCl₃, 300 MHz) δ = 7.26-7.31 (2H, m, arom. H), 7.17-7.21 (3H, m, arom. H), 5.42 (1H, br s, NH), 3.30 (2H, q, *J* = 6.60 Hz, H₁), 2.66 (2H, t, *J* = 7.20 Hz, H₃), 2.11 (2H, t, *J* = 7.50 Hz, H₉), 1.80-1.89 (2H, m, H₂), 1.57-1.70 (2H, m, H₁₀), 0.94 (3H, t, *J* = 7.50 Hz, H₁₁); ¹³C NMR: (CDCl₃, 75.4 MHz) δ = 173.1 (C₈), 141.6 (C₄), 128.6 (C₆), 128.5 (C₅), 126.1 (C₇), 39.3 (C₁), 38.9 (C₉), 33.5 (C₃), 31.4 (C₂), 19.3 (C₁₀), 13.9 (C₁₁); HRMS(ESI-TOF): calcd. for C₁₃H₁₉NOH⁺: 206.1545. Found: 206.1534 (MH⁺), 228.1349 (MNa⁺). CHN: *Anal. Calc.* for C₁₃H₁₉NO: C, 76.06%, H, 9.33%, N, 6.82%; Found: C, 75.90%, H, 9.14%, N, 6.74%.

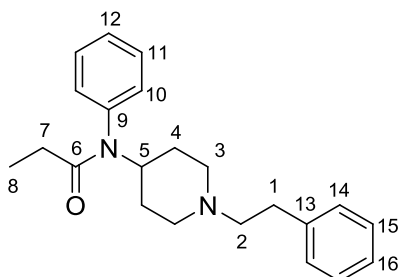
7.4.6 Ruthenium Catalysed Drug Molecule Synthesis under Microwave Conditions

2-(4-(Benzo[*d*][1,3]dioxol-5-ylmethyl)piperazin-1-yl)pyrimidine 4.41

According to representative procedure 7.4.1, the product was purified by silica column chromatography (eluent; Et₂O/petroleum ether b. p. 40-60 °C, 20:1, *R_f* = 0.22, det: KMnO₄) and isolated as a colourless solid (797 mg, 89%). ¹H NMR: (CDCl₃, 300 MHz) δ = 8.29 (2H, d, *J* = 4.80 Hz, H₂), 6.89 (1H, s, H₈), 6.76 (1H, s, H₁₂), 6.76 (1H, s, H₁₁), 6.46 (1H, t, *J* = 4.80 Hz, H₁), 5.95 (2H, s, H₁₃), 3.82 (4H, t, *J* = 5.10 Hz, H₄), 3.46 (2H, s, H₆), 2.48 (4H, t, *J* = 5.10 Hz, H₅); ¹³C NMR: (CDCl₃, 75.4 MHz) δ = 161.8 (C₃), 157.8 (C₂), 147.8 (C₁₀), 146.8 (C₉), 132.0 (C₇), 122.4 (C₁₂),

109.8 (C₁), 109.6 (C₈), 108.0 (C₁₁), 101.0 (C₁₃), 63.0 (C₆), 53.0 (C₅), 43.8 (C₄); HRMS(ESI-TOF): calcd. for C₁₆H₁₉N₄O₂H⁺: 299.1508. Found: 299.1522 (MH⁺). This is consistent with literature data.³¹

N-(1-Phenethylpiperidin-4-yl)-*N*-phenylpropionamide **4.42**



According to representative procedure 7.4.1, the product was purified by silica column chromatography (eluent; Et₂O/hexanes, 4:1, R_f = 0.25, det: KMnO₄) and isolated as a colourless solid (777 mg, 77%). ¹H NMR: (CDCl₃, 300 MHz) δ = 7.35-7.43 (3H, m, arom. H), 7.23-7.29 (2H, m, arom. H), 7.14-7.20 (3H, m, arom. H), 7.07-7.10 (2H, m, arom. H), 4.69 (1H, tt, *J* = 12.20 3.90 Hz, H₅), 3.02 (2H, d, *J* = 11.10 Hz, H₃), 2.72-2.77 (2H, m, H₂), 2.53-2.58 (2H, m, H₁), 2.18 (2H, t, *J* = 11.10 Hz, H₄), 1.93 (2H, q, *J* = 7.50 Hz, H₇), 1.81 (2H, d, *J* = 13.20 Hz, H₃), 1.48 (2H, t, *J* = 12.30 Hz, H₄), 1.01 (3H, t, *J* = 7.50 Hz, H₈); ¹³C NMR: (CDCl₃, 75.4 MHz) δ = 173.7 (C₆), 140.3 (C₁₃), 139.0 (C₉), 130.6 (C₁₁), 129.4 (C₁₅), 128.7 (C₁₄), 128.5 (C₁₀), 128.4 (C₁₂), 126.1 (C₁₆), 60.6 (C₂), 53.2 (C₃), 52.3 (C₅), 33.9 (C₁), 30.7 (C₇), 28.6 (C₄), 9.7 (C₈); HRMS(ESI-TOF): calcd. for C₂₂H₂₈N₂OH⁺: 337.2280. Found: 337.2287 (MH⁺), 359.2096 (MNa⁺). This is consistent with literature data.⁴⁴

7.5 Experimental procedures: Chapter 5

7.5.1 Representative Procedure for the Synthesis of Benzylic Alcohols

To an oven dried, nitrogen purged round bottom flask was added the aldehyde (50 mmol) and THF (100 mL) before cooling to 0 °C using an ice/water bath. Methylmagnesium bromide solution (3.0 M in Et₂O, 19 mL, 57 mmol) was then added dropwise. Once the addition was complete the reaction was allowed to warm to room temperature over 2 hours. NH₄Cl (sat. solution, 50 mL) and H₂O (50 mL) were added before the organic layer was separated. The aqueous layer was then extracted

with EtOAc (2 x 50 mL). The combined organic phase was then dried (MgSO_4) and concentrated *in vacuo*. The crude product was then purified by silica column chromatography.

7.5.2 Representative Procedure for the Tandem Oxidation/C-H

Activation Followed by Reduction

To an oven-dried, nitrogen purged Young's tube containing $\text{Ru}(\text{PPh}_3)_3(\text{CO})(\text{H})_2$ (45.9 mg, 0.05 mmol) were added 1-*m*-tolylethanol (136 mg, 1 mmol), 3,3-dimethylbut-1-ene (0.30 mL, 2.3 mmol) and toluene (1 mL). The reaction vessel was then sealed and heated to 135 °C for 3 hours. On completion the reaction was allowed to cool to room temperature before formic acid (0.19 mL, 5 mmol) was added under nitrogen before the reaction was re-sealed and heated to 135 °C for 3 hours. On completion the reaction was allowed to cool to room temperature and the solvent removed *in vacuo*. The crude product was then purified by silica column chromatography.

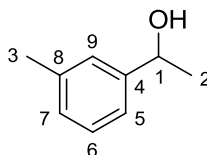
7.5.3 Representative Procedure for the Tandem Oxidation/C-H

Activation

To an oven-dried, nitrogen purged Young's tube containing $\text{Ru}(\text{PPh}_3)_3(\text{CO})(\text{H})_2$ (45.9 mg, 0.05 mmol) were added 1-*m*-tolylethanol (136 mg, 1 mmol), 3,3-dimethylbut-1-ene (0.30 mL, 2.3 mmol) and toluene (1 mL). The reaction vessel was then sealed and heated to 135 °C for 3 hours. On completion the reaction was allowed to cool to room temperature and the solvent removed *in vacuo*. The crude product was then purified by silica column chromatography.

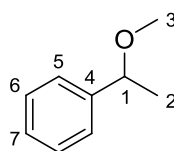
7.5.4 Synthesis of Benzylic Alcohol Starting Materials

1-*m*-Tolylethanol **5.1**

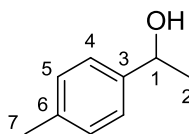


According to representative procedure 7.5.1, the product was purified by silica column chromatography (eluent; cyclohexane/EtOAc, 0-100% over 60 min, R_f = 0.49 in 1:1 cyclohexane/EtOAc, det: KMnO_4) and isolated as a yellow oil (5.72 g, 84%). ^1H NMR: (CDCl_3 , 300 MHz) δ = 7.16-7.28 (3H, m, arom. H), 7.10 (1H, d, J = 7.80 Hz, H_5), 4.87 (1H, q, J = 6.60 Hz, H_1), 2.37 (3H, s, H_3), 1.80 (1H, br s, OH), 1.49 (3H, d, J = 6.60 Hz, H_2); ^{13}C NMR: (CDCl_3 , 75.4 MHz) δ = 145.9 (C_4), 138.3 (C_8), 128.5 (C_6), 128.3 (C_7), 126.2 (C_9), 122.5 (C_5), 70.5 (C_1), 25.2 (C_2), 21.6 (C_3); CHN: *Anal. Calc.* for $\text{C}_9\text{H}_{12}\text{O}$: C, 79.37%, H, 8.88%; Found: C, 79.50%, H, 8.71%. This is consistent with literature data.⁴⁵

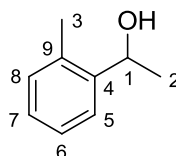
(1-Methoxyethyl)benzene **5.3**



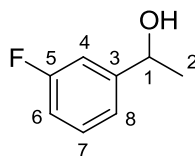
1-Phenylethanol (25 mL, 207 mmol) was dissolved in MeOH (50 mL) before cooling with an ice/water bath. Concentrated H_2SO_4 (12.5 mL) was then added dropwise. After the addition the reaction was heated to 55 °C for 2 hours. The reaction was then allowed to cool to room temperature before the solution was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic phase was then dried (MgSO_4) before concentrating *in vacuo*. The product was then purified by Kugelrohr distillation (5.08 g, 18%) and isolated as a colourless oil. ^1H NMR: (CDCl_3 , 300 MHz) δ = 7.25-7.39 (5H, m, arom. H), 4.30 (1H, q, J = 6.30 Hz, H_1), 3.23 (3H, s, H_3), 1.44 (3H, d, J = 6.30 Hz, H_2); ^{13}C NMR: (CDCl_3 , 75.4 MHz) δ = 143.7 (C_4), 128.6 (C_6), 127.6 (C_7), 126.3 (C_5), 79.8 (C_1), 56.6 (C_3), 24.0 (C_2); HRMS(ESI-TOF): calcd. for $\text{C}_9\text{H}_{12}\text{ONa}^+$: 159.0780. Found: 159.0780 (MNa^+). This is consistent with literature data.⁴⁶

1-*p*-Tolylethanol **5.8**

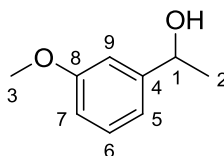
According to representative procedure 7.5.1, the product was purified by silica column chromatography (eluent; petroleum ether b. p. 40-60 °C/Et₂O, 2:1, R_f = 0.24, det: KMnO₄) and isolated as a colourless oil (5.86 g, 86%). ¹H NMR: (CDCl₃, 300 MHz) δ = 7.27 (2H, d, J = 8.10 Hz, H₄), 7.16 (2H, d, J = 8.10 Hz, H₅), 4.88 (1H, q, J = 6.60 Hz, H₁), 2.35 (3H, s, H₇), 1.74 (1H, br s, OH), 1.49 (3H, d, J = 6.60 Hz, H₂); ¹³C NMR: (CDCl₃, 75.4 MHz) δ = 143.0 (C₃), 137.1 (C₆), 129.2 (C₅), 125.4 (C₄), 70.2 (C₁), 25.1 (C₂), 21.2 (C₇); HRMS(ESI-TOF): calcd. for C₉H₁₂OH⁺: 159.0786. Found: 159.0780 (MH⁺). This is consistent with literature data.⁴⁵

1-*o*-Tolylethanol **5.13**

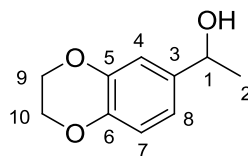
According to representative procedure 7.5.1, the product was purified by silica column chromatography (eluent; cyclohexane/EtOAc, 0-100% over 60 min, R_f = 0.46 in 1:1 cyclohexane/EtOAc, det: KMnO₄) and isolated as a yellow oil (5.92 g, 87%). ¹H NMR: (CDCl₃, 300 MHz) δ = 7.52 (2H, d, J = 7.20 Hz, H₈), 7.13-7.29 (3H, m, arom. H), 5.14 (1H, q, J = 6.60 Hz, H₁), 2.35 (3H, s, H₃), 1.69 (1H, br s, OH), 1.47 (3H, d, J = 6.60 Hz, H₂); ¹³C NMR: (CDCl₃, 75.4 MHz) δ = 144.0 (C₄), 134.3 (C₉), 130.5 (C₈), 127.3 (C₇), 126.5 (C₅), 124.6 (C₆), 66.9 (C₁), 24.0 (C₂), 19.0 (C₃); CHN: *Anal. Calc.* for C₉H₁₂O: C, 79.37%, H, 8.88%; Found: C, 79.40%, H, 8.77%. This is consistent with literature data.⁴⁷

1-(3-Fluorophenyl)ethanol **5.15**

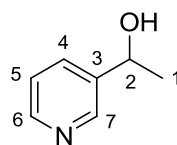
According to representative procedure 7.5.1, the product was purified by silica column chromatography (eluent; petroleum ether b. p. 40-60 °C/Et₂O, 2:1, R_f = 0.24, det: KMnO₄) and isolated as a yellow oil (4.84 g, 69%). ¹H NMR: (CDCl₃, 300 MHz) δ = 7.27-7.34 (1H, m, H₇), 7.08-7.14 (2H, m, H₆ & H₈), 6.92-6.99 (1H, m, H₄), 4.90 (1H, q, J = 6.30 Hz, H₁), 1.74 (1H, br s, OH), 1.49 (3H, d, J = 6.30 Hz, H₂); ¹³C NMR: (CDCl₃, 75.4 MHz) δ = 163.1 (d, J = 245.4 Hz, C₅), 148.7 (d, J = 6.6 Hz, C₃), 130.1 (d, J = 8.1 Hz, C₇), 121.1 (d, J = 2.8 Hz, C₈), 114.3 (d, J = 21.2 Hz, C₆), 112.4 (d, J = 21.8 Hz, C₄), 69.9 (d, J = 1.7 Hz, C₁), 25.3 (C₂); CHN: *Anal. Calc.* for C₈H₉FO: C, 68.56%, H, 6.47%; Found: C, 68.60%, H, 6.60%. This is consistent with literature data.⁴⁵

1-(3-Methoxyphenyl)ethanol **5.16**

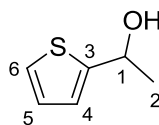
According to representative procedure 7.5.1, the product was purified by silica column chromatography (eluent; cyclohexane/EtOAc, 0-100% over 60 min, R_f = 0.44 in 1:1 cyclohexane/EtOAc, det: KMnO₄) and isolated as a yellow oil (5.25 g, 87%). ¹H NMR: (CDCl₃, 300 MHz) δ = 7.27 (1H, app. t, J = 8.10 Hz, H₆), 6.94-6.96 (2H, m, arom. H), 6.82 (1H, ddd, J = 8.10 2.40 1.20 Hz, H₇), 4.88 (1H, q, J = 6.60 Hz, H₁), 3.82 (3H, s, H₃), 1.74 (1H, br s, OH), 1.50 (3H, d, J = 6.60 Hz, H₂); ¹³C NMR: (CDCl₃, 75.4 MHz) δ = 159.9 (C₈), 147.7 (C₄), 129.6 (C₆), 117.8 (C₅), 113.0 (C₇), 111.0 (C₉), 70.4 (C₁), 55.3 (C₃), 25.2 (C₂); CHN: *Anal. Calc.* for C₉H₁₂O₂: C, 71.03%, H, 7.95%; Found: C, 71.20%, H, 7.85%. This is consistent with literature data.⁴⁸

1-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)ethanol **5.21**

According to representative procedure 7.5.1, the product was purified by silica column chromatography (eluent; petroleum ether b. p. 40-60 °C/Et₂O, 1:1, *R_f* = 0.18, det: KMnO₄) and isolated as a yellow oil (6.76 g, 75%). ¹H NMR: (CDCl₃, 300 MHz) δ = 6.90 (1H, s, H₄), 6.84-6.84 (2H, m, arom. H), 4.80 (1H, q, *J* = 6.30 Hz, H₁), 4.25 (4H, s, H₉ & H₁₀), 1.63 (1H, br s, OH), 1.46 (3H, d, *J* = 6.30 Hz, H₂); ¹³C NMR: (CDCl₃, 75.4 MHz) δ = 143.5 (C₆), 142.9 (C₅), 139.5 (C₃), 118.6 (C₈), 117.3 (C₇), 114.5 (C₄), 70.0 (C₁), 64.5 (C₉), 64.5 (C₁₀), 25.1 (C₂); CHN: *Anal. Calc.* for C₁₀H₁₂O₃: C, 66.65%, H, 6.71%; Found: C, 66.60%, H, 6.62%. This is consistent with literature data.⁴⁹

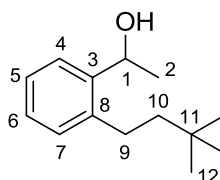
1-(Pyridin-3-yl)ethanol **5.23**

According to representative procedure 7.5.1, the product was purified by silica column chromatography (eluent; EtOAc/MeOH, 20:1, *R_f* = 0.24, det: KMnO₄) and isolated as a yellow oil (5.11 g, 83%). ¹H NMR: (CDCl₃, 300 MHz) δ = 8.56 (1H, d, *J* = 2.10 Hz, H₇), 8.49 (1H, dd, *J* = 4.80 1.50 Hz, H₆), 7.72-7.76 (1H, m, H₄), 7.28 (1H, ddd, *J* = 7.80 4.80 0.60 Hz, H₅), 4.95 (1H, q, *J* = 6.60 Hz, H₂), 2.53 (1H, br s, OH), 1.52 (3H, d, *J* = 6.60 Hz, H₁); ¹³C NMR: (CDCl₃, 75.4 MHz) δ = 148.1 (C₇), 147.1 (C₆), 141.8 (C₃), 133.6 (C₄), 123.7 (C₅), 67.6 (C₂), 25.3 (C₁); HRMS(ESI-TOF): calcd. for C₇H₁₀NOH⁺: 124.0762. Found: 124.0763 (MH⁺). This is consistent with literature data.⁵⁰

1-(Thiophen-2-yl)ethanol **5.24**

According to representative procedure 7.5.1, the product was purified by silica column chromatography (eluent; petroleum ether b. p. 40-60 °C/Et₂O, 2:1, R_f = 0.21, det: KMnO₄) and isolated as a yellow oil (5.06 g, 79%). ¹H NMR: (CDCl₃, 300 MHz) δ = 7.24 (1H, dd, J = 4.80 1.50 Hz, H₆), 6.95-7.00 (2H, m, H₄ & H₅), 5.14 (1H, q, J = 6.30 Hz, H₁), 1.93 (1H, br s, OH), 1.61 (3H, d, J = 6.30 Hz, H₂); ¹³C NMR: (CDCl₃, 75.4 MHz) δ = 150.0 (C₃), 126.8 (C₆), 124.6 (C₅), 123.3 (C₄), 66.4 (C₁), 25.4 (C₂); CHN: calcd. for C₆H₈OSH⁺: 151.0188. Found: 151.0188 (MNa⁺). This is consistent with literature data.⁵¹

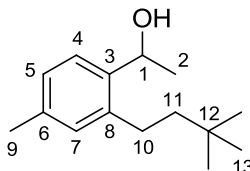
7.5.5 Ruthenium-Catalysed Synthesis of Alkylated Benzylic Alcohols Using A Tandem Oxidation/C-H Activation Process Followed by Reduction

1-(2-(3,3-Dimethylbutyl)phenyl)ethanol **5.10**

According to representative procedure 7.5.2, the product was purified by silica column chromatography (eluent; petroleum ether b. p. 40-60 °C/Et₂O, 4:1, R_f = 0.21, det: KMnO₄) and isolated as a brown oil (157 mg, 76%). IR: ν_{\max} /cm⁻¹ (neat) 3351, 2953, 1467, 1364, 1246, 1075, 1003, 756; ¹H NMR: (CDCl₃, 300 MHz) δ = 7.51-7.54 (1H, m, H₆), 7.12-7.24 (3H, m, arom. H), 5.17 (1H, q, J = 6.60 Hz, H₁), 2.61 (2H, t, J = 8.70 Hz, H₉), 1.61 (1H, br s, OH), 1.51 (3H, d, J = 6.60 Hz, H₂), 1.41-1.473 (2H, m, H₁₀), 0.98 (9H, s, H₁₂); ¹³C NMR: (CDCl₃, 75.4 MHz) δ = 143.4 (C₃), 139.9 (C₈), 129.6 (C₇), 127.5 (C₆), 126.5 (C₅), 125.1 (C₄), 66.3 (C₁), 46.8 (C₁₀), 30.8 (C₁₁), 29.4 (C₁₂), 27.7 (C₉), 25.0 (C₂); HRMS(ESI-TOF): calcd. for C₁₄H₂₂ONa⁺: 229.1568.

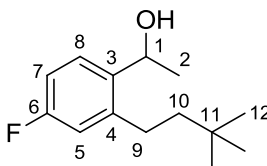
Found: 229.1560 (MNa^+); CHN: *Anal. Calc.* for $\text{C}_{14}\text{H}_{22}\text{O}$: C, 81.50%, H, 10.75%;
Found: C, 81.40%, H, 10.60%.

1-(2-(3,3-Dimethylbutyl)-4-methylphenyl)ethanol **5.11**



According to representative procedure 7.5.2, the product was purified by silica column chromatography (eluent; petroleum ether b. p. 40-60 °C/Et₂O, 4:1, R_f = 0.21, det: KMnO_4) and isolated as a yellow oil (123 mg, 56%). IR: $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3351, 2953, 1466, 1364, 1076, 1007, 890, 820; ^1H NMR: (CDCl_3 , 300 MHz) δ = 7.41 (1H, d, J = 8.10 Hz, H_4), 7.04 (1H, d, J = 8.10 Hz, H_5), 6.96 (1H, s, H_7), 5.13 (1H, q, J = 6.30 Hz, H_1), 2.58 (2H, t, J = 8.70 Hz, H_{10}), 2.31 (3H, s, H_9), 1.57 (1H, br s, OH), 1.49 (3H, d, J = 6.30 Hz, H_2), 1.40-1.46 (2H, m, H_{11}), 0.98 (9H, s, H_{13}); ^{13}C NMR: (CDCl_3 , 75.4 MHz) δ = 140.4 (C_6), 139.9 (C_3), 137.1 (C_8), 130.3 (C_7), 127.2 (C_4), 125.2 (C_5), 66.2 (C_1), 46.9 (C_{11}), 30.8 (C_{12}), 29.4 (C_{13}), 27.7 (C_{10}), 24.9 (C_2), 21.2 (C_9); HRMS(ESI-TOF): calcd. for $\text{C}_{15}\text{H}_{24}\text{ONa}^+$: 243.1725. Found: 243.1727 (MNa^+); CHN: *Anal. Calc.* for $\text{C}_{15}\text{H}_{24}\text{O}$: C, 81.76%, H, 10.98%; Found: C, 81.63%, H, 10.80%.

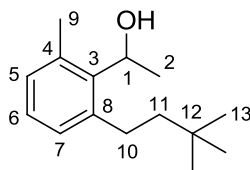
1-(2-(3,3-Dimethylbutyl)-4-fluorophenyl)ethanol **5.12**



According to representative procedure 7.5.2, the product was purified by silica column chromatography (eluent; petroleum ether b. p. 40-60 °C/Et₂O, 3:1, R_f = 0.23, det: KMnO_4) and isolated as a yellow oil (139 mg, 62%). IR: $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3351, 2954, 1613, 1591, 1497, 1365, 1239, 1074, 865, 819; ^1H NMR: (CDCl_3 , 300 MHz) δ = 7.49 (1H, dd, J = 8.40 6.00 Hz, H_8), 6.82-6.94 (2H, m, H_5 & H_7), 5.12 (1H, dq, J = 6.60 3.00 Hz, H_1), 2.59 (2H, t, J = 8.85 Hz, H_9), 1.63 (1H, d, J = 3.30 Hz, OH), 1.48 (3H, d, J = 6.60 Hz, H_2), 1.36-1.51 (2H, m, H_{10}), 0.98 (9H, s, H_{12}); ^{13}C NMR: (CDCl_3 ,

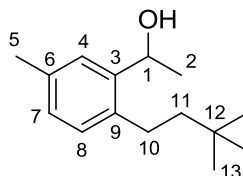
75.4 MHz) δ = 162.1 (d, J = 244.7 Hz, C₆), 142.4 (d, J = 7.1 Hz, C₄), 139.1 (d, J = 3.0 Hz, C₃), 127.0 (d, J = 8.4 Hz, C₈), 115.8 (d, J = 23.0 Hz, C₅), 113.1 (d, J = 20.9 Hz, C₇), 65.9 (C₁), 46.3 (C₁₀), 30.8 (C₁₁), 29.3 (C₁₂), 27.7 (d, J = 1.28 Hz, C₉), 25.1 (C₂); ¹⁹F NMR: (CDCl₃, 376 MHz) δ = -619.4 (ddd, J = 9.8, 8.3, 6.0 Hz); HRMS(ESI-TOF): calcd. for C₁₄H₂₁OFNa⁺: 247.1474. Found: 247.1463 (MNa⁺); CHN: *Anal.* *Calc.* for C₁₄H₂₁OF: C, 74.96%, H, 9.44%; Found: C, 75.00%, H, 9.24%.

1-(2-(3,3-Dimethylbutyl)-6-methylphenyl)ethanol **5.17**



According to representative procedure 7.5.2, the product was purified by silica column chromatography (eluent; petroleum ether b. p. 40-60 °C/Et₂O, 5:1, R_f = 0.23, det: KMnO₄) and isolated as a yellow oil (90 mg, 41%). IR: $\nu_{\max}/\text{cm}^{-1}$ (neat) 3350, 2952, 1465, 1364, 109, 893, 756; ¹H NMR: (CDCl₃, 300 MHz) δ = 7.08 (1H, dd, J = 7.50 6.90 Hz, H₆), 6.98-7.00 (2H, m, H₅ & H₇), 5.39 (1H, qd, J = 6.90 2.40 Hz, H₁), 2.63-2.79 (2H, m, H₁₀), 2.50 (3H, s, H₉), 1.68 (1H, d, J = 2.70 Hz, OH), 1.58 (3H, d, J = 6.90 Hz, H₂), 1.45 (2H, dd, J = 9.60 8.10 Hz, H₁₁), 0.98 (9H, s, H₁₃); ¹³C NMR: (CDCl₃, 75.4 MHz) δ = 141.4 (C₄), 140.2 (C₃), 136.4 (C₈), 129.7 (C₅), 128.6 (C₆), 127.3 (C₇), 67.5 (C₁), 47.4 (C₁₁), 30.9 (C₁₂), 29.4 (C₁₃), 29.0 (C₁₀), 22.6 (C₂), 20.9 (C₉); HRMS(ESI-TOF): calcd. for C₁₅H₂₄ONa⁺: 243.1725. Found: 243.1718 (MNa⁺); CHN: *Anal.* *Calc.* for C₁₅H₂₄O: C, 81.76%, H, 10.98%; Found: C, 81.60%, H, 11.10%.

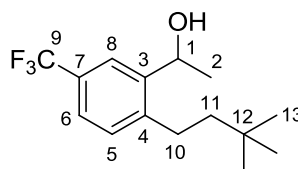
1-(2-(3,3-Dimethylbutyl)-5-methylphenyl)ethanol **5.3**



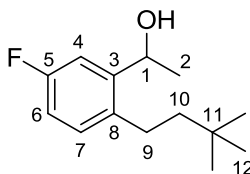
According to representative procedure 7.5.2, the product was purified by silica column chromatography (eluent; petroleum ether b. p. 40-60 °C/Et₂O, 4:1, R_f = 0.21,

det: KMnO_4) and isolated as a brown oil (159 mg, 72%). IR: $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3336, 2954, 1467, 1364, 1246, 1074, 1026, 823; ^1H NMR: (CDCl_3 , 300 MHz) δ = 7.34 (1H, s, H_4), 7.03 (2H, s, H_7 & H_8), 5.14 (1H, q, J = 6.30 Hz, H_1), 2.57 (2H, t, J = 8.85 Hz, H_{10}), 2.33 (3H, s, H_5), 1.61 (1H, br s, OH), 1.49 (3H, d, J = 6.30 Hz, H_2), 1.39-1.47 (2H, m, H_{11}), 0.98 (9H, s, H_{13}); ^{13}C NMR: (CDCl_3 , 75.4 MHz) δ = 143.1 (C_1), 136.8 (C_6), 135.9 (C_9), 129.6 (C_8), 128.3 (C_4), 125.7 (C_7), 66.3 (C_1), 47.0 (C_{11}), 30.8 (C_{12}), 29.4 (C_{13}), 27.3 (C_{10}), 25.0 (C_2), 21.3 (C_5); HRMS(ESI-TOF): calcd. for $\text{C}_{15}\text{H}_{24}\text{ONa}^+$: 243.1722. Found: 243.1725 (MNa^+); CHN: *Anal. Calc.* for $\text{C}_{15}\text{H}_{24}\text{O}$: C, 81.76%, H, 10.98%; Found: C, 81.72%, H, 10.80%.

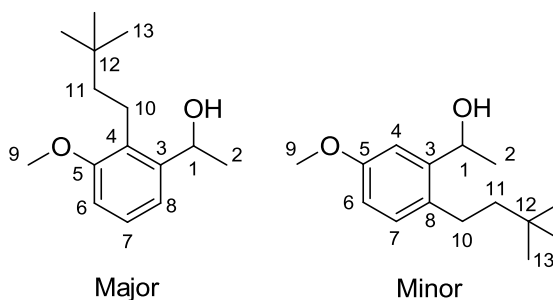
1-(2-(3,3-Dimethylbutyl)-5-(trifluoromethyl)phenyl)ethanol **5.18**



According to representative procedure 7.5.2, the product was purified by silica column chromatography (eluent; petroleum ether b. p. 40-60 °C/ Et_2O , 6:1, R_f = 0.20, det: KMnO_4) and isolated as a brown solid (239 mg, 87%). m. p. = 61-63 °C; IR: $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3353, 3288, 2954, 1366, 1324, 1149, 1129, 1116, 1087, 916, 830; ^1H NMR: (CDCl_3 , 300 MHz) δ = 7.81 (1H, s, H_8), 7.44 (1H, dd, J = 8.10 1.50 Hz, H_6), 7.24 (1H, d, J = 8.10 Hz, H_5), 5.19 (1H, q, J = 6.60 Hz, H_1), 2.64 (2H, t, J = 8.85 Hz, H_{10}), 1.62 (1H, br s, OH), 1.41-1.49 (2H, m, H_{11}), 0.99 (9H, s, H_{13}); ^{13}C NMR: (CDCl_3 , 75.4 MHz) δ = 144.2 (C_4), 143.8 (d, J = 1.1 Hz, C_3), 130.0 (C_5), 128.8 (d, J = 32.3 Hz, C_7), 124.5 (q, J = 271.7 Hz, C_9), 124.2 (q, J = 3.8 Hz, C_8), 122.3 (q, J = 3.9 Hz, C_6), 66.1 (C_1), 46.4 (C_{11}), 30.9 (C_{12}), 29.3 (C_{13}), 27.7 (C_{10}), 25.1 (C_2); ^{19}F NMR: (CDCl_3 , 376 MHz) δ = -62.4 (s); HRMS(ESI-TOF): calcd. for $\text{C}_{15}\text{H}_{21}\text{OF}_3\text{Na}^+$: 297.1437. Found: 297.1437 (MNa^+); CHN: *Anal. Calc.* for $\text{C}_{15}\text{H}_{21}\text{OF}_3$: C, 65.67%, H, 7.72%; Found: C, 65.70%, H, 7.73%.

1-(2-(3,3-Dimethylbutyl)-5-fluorophenyl)ethanol **5.19**

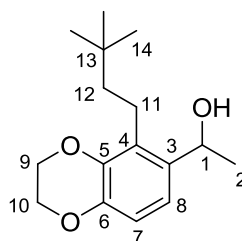
According to representative procedure 7.5.2, the product was purified by silica column chromatography (eluent; petroleum ether b. p. 40-60 °C/Et₂O, 4:1, R_f = 0.19, det: KMnO₄) and isolated as a brown oil (139 mg, 62%). IR: $\nu_{\max}/\text{cm}^{-1}$ (neat) 3345, 2956, 1463, 1365, 1243, 1061, 864, 793; ¹H NMR: (CDCl₃, 300 MHz) δ = 7.32 (1H, d, J = 7.80 Hz, H₇), 7.15-7.22 (1H, m, H₆), 6.93 (1H, app. t, J = 9.00 Hz, H₄), 5.13 (1H, q, J = 6.30 Hz, H₁), 2.52-2.75 (2H, m, H₉), 1.60 (1H, br s, OH), 1.50 (3H, d, J = 6.30 Hz, H₂), 1.37-1.44 (2H, m, H₁₀), 0.99 (9H, s, H₁₂); ¹³C NMR: (CDCl₃, 75.4 MHz) δ = 161.2 (d, J = 243.6 Hz, C₅), 145.8 (d, J = 3.8 Hz, C₃), 127.4 (d, J = 15.5 Hz, C₆), 127.3 (d, J = 9.0 Hz, C₇), 120.7 (d, J = 3.1 Hz, C₈), 114.1 (d, J = 23.1 Hz, C₄), 66.2 (d, J = 3.10 Hz, C₁), 45.0 (C₁₀), 30.9 (C₁₁), 29.2 (C₁₂), 25.1 (C₂), 20.3 (d, J = 4.3 Hz, C₉); ¹⁹F NMR: (CDCl₃, 376 MHz) δ = - 118.7 (dddt, J = 9.8, 5.6, 1.9 Hz); HRMS(ESI-TOF): calcd. for C₁₄H₂₁OFNa⁺: 247.1474. Found: 247.1481 (MNa⁺); CHN: *Anal. Calc.* for C₁₄H₂₁OF: C, 74.96%, H, 9.44%; Found: C, 75.10%, H, 9.33%.

1-(2-(3,3-Dimethylbutyl)-5-methoxyphenyl)ethanol **5.20**

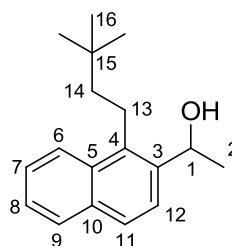
According to representative procedure 7.5.2, the product was purified by silica column chromatography (eluent; petroleum ether b. p. 40-60 °C/Et₂O, 7:2, R_f = 0.22, det: KMnO₄) and isolated as a yellow oil (147 mg, 70%). IR: $\nu_{\max}/\text{cm}^{-1}$ (neat) 3226, 2950, 1585, 1466, 1362, 1260, 1245, 1071, 1009, 847, 788, 725; ¹H NMR: (CDCl₃, 300 MHz) δ = 7.13-7.21 (2H, m, arom. H), 6.76-6.79 (1H, m, arom. H), 5.15 (1H, q, J = 6.30 Hz, H₁), 3.82 (3H, s, H₉), 2.51-2.75 (2H, m, H₁₀), 1.64 (1H, br s, OH), 1.49 (3H, d, J = 6.30 Hz, H₂), 1.31-1.41 (2H, m, H₁₁), 0.98 (9H, s, H₁₃); Minor 7.04-7.23 (2H, m, arom. H), 6.74-6.77 (1H, m, arom. H), 5.15 (1H, q, J = 6.30 Hz, H₁), 3.81

(3H, s, H₉), 2.51-2.75 (2H, m, H₁₀), 1.64 (1H, br s, OH), 1.49 (3H, d, $J = 6.30$ Hz, H₂), 1.31-1.41 (2H, m, H₁₁), 0.97 (9H, s, H₁₃); ¹³C NMR: (CDCl₃, 75.4 MHz) δ = Major 157.4 (C₅), 144.8 (C₃), 128.7 (C₇), 126.9 (C₄), 117.2 (C₈), 109.4 (C₆), 66.4 (C₁), 55.7 (C₉), 44.5 (C₁₁), 30.9 (C₁₂), 29.3 (C₁₃), 25.1 (C₂), 20.7 (C₁₀); Minor 158.3 (C₅), 131.8 (C₃), 130.6 (C₇), 128.7 (C₈), 113.2 (C₆), 110.4 (C₄), 66.4 (C₁), 55.4 (C₉), 47.0 (C₁₁), 30.8 (C₁₂), 29.4 (C₁₃), 26.9 (C₁₀), 25.1 (C₂); HRMS(ESI-TOF): calcd. for C₁₅H₂₄O₂Na⁺: 259.1674. Found: 259.1654 (MNa⁺); CHN: *Anal. Calc.* for C₁₅H₂₄O₂: C, 76.23%, H, 10.24%; Found: C, 76.20%, H, 10.40%.

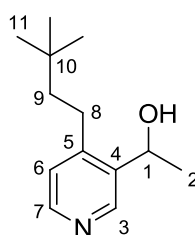
1-(5-(3,3-Dimethylbutyl)-2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)ethanol **5.25**



According to representative procedure 7.5.2, the product was purified by silica column chromatography (eluent; petroleum ether b. p. 40-60 °C/Et₂O, 2:1, R_f = 0.23, det: KMnO₄) and isolated as a brown solid (139 mg, 53%). m. p. = 69-71 °C; IR: $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3317, 2958, 2866, 2160, 2032, 1978, 1606, 1487, 1435, 1367, 1283, 1072; ¹H NMR: (CDCl₃, 300 MHz) δ = 7.02 (1H, d, $J = 8.70$ Hz, H₈), 6.76 (1H, d, $J = 8.70$ Hz, H₇), 5.06 (1H, q, $J = 6.30$ Hz, H₁), 4.21-4.28 (4H, m, H₉ & H₁₀), 2.51-2.70 (2H, m, H₁₁), 1.57 (1H, br s, OH), 1.47 (3H, d, $J = 6.30$ Hz, H₂), 1.31-1.40 (2H, m, H₁₂), 0.98 (9H, s, H₁₄); ¹³C NMR: (CDCl₃, 75.4 MHz) δ = 142.6 (C₅), 141.0 (C₆), 136.6 (C₃), 129.4 (C₄), 117.6 (C₈), 115.0 (C₇), 66.1 (C₁), 64.4 (C₉), 64.3 (C₁₀), 44.5 (C₁₂), 30.9 (C₁₃), 29.3 (C₁₄), 24.9 (C₂), 20.6 (C₁₁); HRMS(ESI-TOF): calcd. for C₁₆H₂₄O₃Na⁺: 287.1623. Found: 287.1617 (MNa⁺); CHN: *Anal. Calc.* for C₁₆H₂₄O₃: C, 72.69%, H, 9.15%; Found: C, 72.80%, H, 9.20%.

1-(1-(3,3-Dimethylbutyl)naphthalen-2-yl)ethanol **5.26**

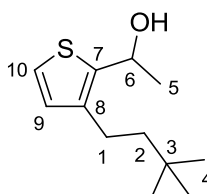
According to representative procedure 7.5.2, the product was purified by silica column chromatography (eluent; petroleum ether b. p. 40-60 °C/Et₂O, 3:1, R_f = 0.25, det: KMnO₄) and isolated as a brown solid (228 mg, 89%). m. p. = 98-100 °C; IR: $\nu_{\max}/\text{cm}^{-1}$ (neat) 3282, 2948, 2905, 2865, 1478, 1364, 1284, 1101, 1067, 818, 745; ¹H NMR: (CDCl₃, 300 MHz) δ = 8.03 (1H, d, J = 8.40 Hz, H₆), 7.69-7.84 (3H, m, arom. H), 7.43-7.54 (2H, m, arom. H), 5.42 (1H, q, J = 6.30 Hz, H₁), 2.98-3.18 (2H, m, H₁₃), 1.61 (1H, br s, OH), 1.57 (3H, d, J = 6.30 Hz, H₂), 1.45-1.62 (2H, m, H₁₄), 1.08 (9H, s, H₁₆); ¹³C NMR: (CDCl₃, 75.4 MHz) δ = 140.0 (C₃), 134.6 (C₄), 133.4 (C₅), 131.9 (C₁₀), 128.8 (C₉), 127.1 (C₁₂), 126.2 (C₁₁), 125.4 (C₇), 124.1 (C₆), 123.3 (C₈), 66.6 (C₁), 45.5 (C₁₄), 31.2 (C₁₅), 29.4 (C₁₆), 25.1 (C₂), 22.9 (C₁₃); HRMS(ESI-TOF): calcd. for C₁₈H₂₄ONa⁺: 279.1725. Found: 279.1717 (MNa⁺); CHN: *Anal. Calc.* for C₁₈H₂₄O: C, 84.32%, H, 9.44%; Found: C, 84.30%, H, 9.44%.

1-(4-(3,3-Dimethylbutyl)pyridine-3-yl)ethanol **5.27**

According to representative procedure 7.5.2, the product was purified by silica column chromatography (eluent; Et₂O, R_f = 0.16, det: KMnO₄) and isolated as a colourless oil (114 mg, 55%). IR: $\nu_{\max}/\text{cm}^{-1}$ (neat) 3220, 2953, 1600, 1365, 1096, 1067, 904, 730; ¹H NMR: (CDCl₃, 300 MHz) δ = 8.49 (1H, s, H₃), 8.12 (1H, d, J = 5.10 Hz, H₇), 6.94 (1H, d, J = 5.10 Hz, H₆), 5.07 (1H, q, J = 6.30 Hz, H₁), 4.87 (1H, br s, OH), 2.53 (2H, t, J = 8.70 Hz, H₈), 1.45 (3H, d, J = 6.30 Hz, H₂), 1.30-1.41 (2H, m, H₉), 0.90 (9H, s, H₁₁); ¹³C NMR: (CDCl₃, 75.4 MHz) δ = 149.3 (C₃), 147.4 (C₇), 147.2 (C₄), 139.6 (C₅), 124.0 (C₆), 64.6 (C₁), 45.3 (C₉), 30.7 (C₁₀), 29.2 (C₁₁), 26.9

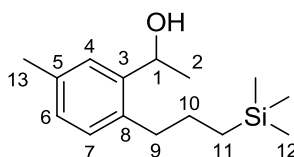
(C₈), 24.9 (C₂); HRMS(ESI-TOF): calcd. for C₁₃H₂₁NOH⁺: 208.1701. Found: 208.1695 (MH⁺); CHN: *Anal. Calc.* for C₁₃H₂₁NO: C, 75.32%, H, 10.21%, N, 6.76%; Found: C, 75.40%, H, 10.30%, N, 6.86%.

1-(3-(3,3-Dimethylbutyl)thiophen-2-yl)ethanol **5.28**



According to representative procedure 7.5.2, the product was purified by silica column chromatography (eluent; petroleum ether b. p. 40-60 °C/Et₂O, 5:1, R_f = 0.22, det: KMnO₄) and isolated as a brown oil (117 mg, 55%). IR: $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3354, 2953, 1467, 1364, 1064, 883, 716, 656; ¹H NMR: (CDCl₃, 300 MHz) δ = 7.15 (1H, d, *J* = 5.10 Hz, H₁₀), 6.83 (1H, d, *J* = 5.10 Hz, H₉), 5.21 (1H, q, *J* = 6.60 Hz, H₆), 2.53-2.59 (2H, m, H₁), 1.69 (1H, br s, OH), 1.58 (2H, d, *J* = 6.60 Hz, H₅), 1.41-1.49 (2H, m, H₂), 0.96 (9H, s, H₄); ¹³C NMR: (CDCl₃, 75.4 MHz) δ = 142.6 (C₇), 139.1 (C₈), 129.1 (C₁₀), 123.1 (C₉), 64.4 (C₆), 45.8 (C₂), 30.7 (C₃), 29.4 (C₄), 25.5 (C₁), 23.7 (C₅); HRMS(ESI-TOF): calcd. for C₁₂H₂₀OSNa⁺: 235.1127. Found: 235.1127 (MNa⁺); CHN: *Anal. Calc.* for C₁₂H₂₀OS: C, 67.87%, H, 9.49%; Found: C, 67.70%, H, 9.39%.

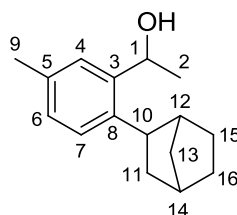
1-(5-Methyl-2-(3-(trimethylsilyl)propyl)phenyl)ethanol **5.39**



According to representative procedure 7.5.2, the product was purified by silica column chromatography (eluent; petroleum ether b. p. 40-60 °C/Et₂O, 6:1, R_f = 0.20, det: KMnO₄) and isolated as a brown oil (170 mg, 68%). IR: $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3363, 2952, 1247, 1072, 833, 691; ¹H NMR: (CDCl₃, 300 MHz) δ = 7.35 (1H, s, H₄), 7.00-7.06 (2H, m, arom. H), 5.16 (1H, q, *J* = 6.60 Hz, H₁), 2.63 (2H, t, *J* = 7.80 Hz, H₉), 2.34 (3H, s, H₁₃), 1.62 (1H, br s, OH), 1.49-1.60 (2H, m, H₁₀), 1.48 (3H, d, *J* = 6.60 Hz, H₂), 0.56-0.61 (2H, m, H₁₁), -0.02 (9H, s, H₁₂); ¹³C NMR: (CDCl₃, 75.4 MHz) δ =

143.3 (C₃), 136.1 (C₅), 136.0 (C₈), 129.6 (C₇), 128.2 (C₄), 125.7 (C₆), 66.4 (C₁), 36.1 (C₉), 29.6 (C₁₀), 25.0 (C₂), 21.3 (C₁₃), 17.2 (C₁₁), -1.54 (C₁₂); HRMS(ESI-TOF): calcd. for C₁₅H₂₆OSiNa⁺: 273.1651. Found: 273.1653 (MNa⁺); CHN: *Anal. Calc.* for C₁₅H₂₆O: C, 71.93%, H, 10.46%; Found: C, 71.90%, H, 10.46%.

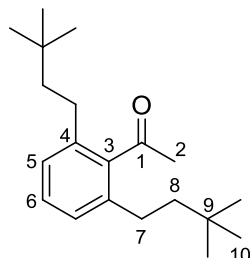
1-(2-(Bicyclo[2.2.1]heptan-2-yl)-5-methylphenyl)ethanol **5.40**



According to representative procedure 7.5.2, the product was purified by silica column chromatography (eluent; petroleum ether b. p. 40-60 °C/Et₂O, 3:1, R_f = 0.20, det: KMnO₄) and isolated as an off-white solid oil (193 mg, 84%). IR: $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3314, 2945, 2866, 1499, 1451, 1365, 1289, 1075, 811; ¹H NMR: (CDCl₃, 300 MHz) δ = 7.36 (1H, m, H₄), 7.16 (1H, dd, *J* = 7.80 0.90 Hz, H₇), 7.04 (1H, dd, *J* = 8.10, 0.60 Hz, H₆), 5.18 (1H, q, *J* = 6.30 Hz, H₁), 2.87 (1H, m, H₁₀), 2.36 (1H, br s, OH), 2.33 (3H, s, H₉), 1.53-1.90 (7H, m, alk. H), 1.48 (3H, dd, *J* = 6.30 3.30 Hz, H₂), 1.24-1.40 (3H, m, alk. H); Analysis of the ¹³C NMR showed that the two diastereomers were clearly visible. Both diastereomers are reported here. ¹³C NMR: (CDCl₃, 75.4 MHz) δ = 143.5 & 143.4 (C₈), 140.9 & 140.7 (C₃), 135.5 (C₅), 128.1 & 128.1 (C₄), 126.1 & 125.9 (C₆), 125.3 & 125.2 (C₇), 66.2 & 66.1 (C₁), 42.6 & 42.4 (C₁₀), 42.4 & 42.2 (C₁₂), 40.5 & 40.4 (C₁₁), 37.1 & 37.0 (C₁₄), 36.7 & 36.7 (C₁₃), 30.9 & 30.8 (C₁₆), 29.0 (C₁₅), 25.0 & 24.8 (C₂), 21.1 (C₉); HRMS(ESI-TOF): calcd. for C₁₆H₂₂ONa⁺: 253.1568. Found: 253.1565 (MNa⁺); CHN: *Anal. Calc.* for C₁₆H₂₂O: C, 83.43%, H, 9.63%; Found: C, 83.49%, H, 9.62%.

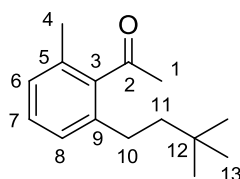
7.6.5 Ruthenium-Catalysed Synthesis of Alkylated Aromatic Ketones Using A Tandem Oxidation/C-H Activation Process

1-(2,6-Bis(3,3-dimethylbutyl)phenyl)ethanone **5.29**



According to representative procedure 7.5.3, the product was purified by silica column chromatography (eluent; petroleum ether b. p. 40-60 °C/Et₂O, 20:1, *R_f* = 0.20, det: KMnO₄) and isolated as a brown oil (283 mg, 98%). IR: $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 2953, 1699, 1464, 1364, 1246, 758; ¹H NMR: (CDCl₃, 300 MHz) δ = 7.21 (1H, t, *J* = 7.50 Hz, H₆), 7.03 (2H, d, *J* = 7.50 Hz, H₅), 2.50 (3H, s, H₂), 2.41-2.47 (4H, m, H₇), 1.43-1.49 (4H, m, H₈), 0.93 (18H, s, H₁₀); ¹³C NMR: (CDCl₃, 75.4 MHz) δ = 208.2 (C₁), 142.1 (C₃), 138.0 (C₄), 128.8 (C₆), 126.9 (C₅), 46.7 (C₈), 33.2 (C₂), 30.7 (C₉), 29.3 (C₁₀), 28.7 (C₇); HRMS(ESI-TOF): calcd. for C₂₀H₃₂O⁺: 289.2531. Found: 289.2531 (MH⁺), 311.2338 (MNa⁺); CHN: *Anal. Calc.* for C₂₀H₃₂O: C, 83.27%, H, 11.18%; Found: C, 83.16%, H, 11.10%.

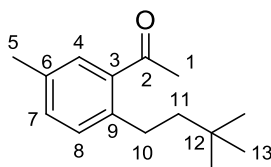
1-(2-(3,3-Dimethylbutyl)-6-methylphenyl)ethanone **5.30**



According to representative procedure 7.5.3, the product was purified by silica column chromatography (eluent; petroleum ether b. p. 40-60 °C/Et₂O, 20:1, *R_f* = 0.21, det: KMnO₄) and isolated as a brown oil (212 mg, 97%). ¹H NMR: (CDCl₃, 300 MHz) δ = 7.16-7.21 (1H, m, H₇), 7.00-7.05 (2H, m, arom. H), 2.49 (3H, s, H₁), 2.42-2.48 (2H, m, H₁₀), 2.25 (3H, s, H₄), 1.42-1.48 (2H, m, H₁₁), 0.93 (9H, s, H₁₃); ¹³C NMR: (CDCl₃, 75.4 MHz) δ = 208.4 (C₂), 142.4 (C₃), 138.1 (C₉), 132.2 (C₅), 128.7

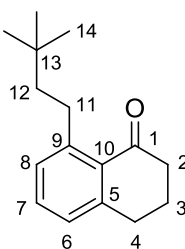
(C₇), 127.8 (C₆), 127.0 (C₈), 46.7 (C₁₁), 32.7 (C₁), 30.7 (C₁₂), 29.3 (C₁₃), 28.6 (C₁₀), 19.3 (C₄); HRMS(ESI-TOF): calcd. for C₁₅H₂₂OH⁺: 219.1749. Found: 219.1742 (MH⁺). This is consistent with literature data.⁵²

1-(2-(3,3-Dimethylbutyl)-5-methylphenyl)ethanone **5.31**



According to representative procedure 7.5.3, the product was purified by silica column chromatography (eluent; petroleum ether b. p. 40-60 °C/Et₂O, 20:1, R_f = 0.21, det: KMnO₄) and isolated as a brown oil (210 mg, 96%). IR: ν_{max} /cm⁻¹ (neat) 2953, 1685, 1467, 1354, 1264, 1186, 951, 828, 619; ¹H NMR: (CDCl₃, 300 MHz) δ = 7.41 (1H, s, H₄), 7.20 (1H, dd, *J* = 7.80 1.50 Hz, H₇), 7.13 (1H, d, *J* = 7.80 Hz, H₈), 2.73-2.79 (2H, m, H₁₀), 2.57 (3H, s, H₁), 2.36 (3H, s, H₅), 1.38-1.44 (2H, m, H₁₁), 0.96 (9H, s, H₁₃); ¹³C NMR: (CDCl₃, 75.4 MHz) δ = 202.4 (C₂), 140.6 (C₃), 138.1 (C₉), 135.1 (C₆), 132.2 (C₇), 131.3 (C₈), 129.7 (C₄), 46.7 (C₁₁), 30.8 (C₁₂), 30.0 (C₁), 29.4 (C₁₃), 21.0 (C₅); HRMS(ESI-TOF): calcd. for C₁₅H₂₂ONa⁺: 241.1568. Found: 241.1554 (MNa⁺); CHN: *Anal. Calc.* for C₁₅H₂₂O: C, 82.52%, H, 10.16%; Found: C, 82.50%, H, 9.96%.

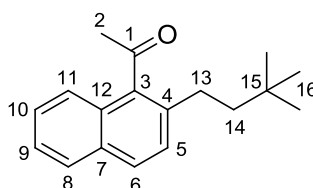
8-(3,3-Dimethylbutyl)-3,4-dihydronaphthalen-1(2*H*)-one **5.32**



According to representative procedure 7.5.3, the product was purified by silica column chromatography (eluent; petroleum ether b. p. 40-60 °C/Et₂O, 17:1, R_f = 0.19, det: KMnO₄) and isolated as a brown oil (187 mg, 81%). ¹H NMR: (CDCl₃, 300 MHz) δ = 7.32 (1H, dd, *J* = 7.80 7.20 Hz, H₇), 7.09 (1H, d, *J* = 7.80 Hz, H₆), 7.08 (1H, d, *J* = 7.80 Hz, H₈), 2.93-3.03 (4H, m, H₄ & H₁₁), 2.65 (2H, t, *J* = 6.60 Hz, H₂),

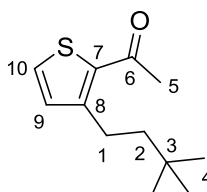
2.03-2.12 (2H, m, H₃), 1.40-1.46 (2H, m, H₁₂), 1.00 (9H, s, H₁₄); ¹³C NMR: (CDCl₃, 75.4 MHz) δ = 200.0 (C₁), 147.2 (C₁₀), 146.0 (C₉), 132.4 (C₇), 131.1 (C₅), 130.1 (C₈), 126.8 (C₆), 46.1 (C₁₂), 41.3 (C₂), 31.3 (C₄), 30.9 (C₁₃), 30.9 (C₁₁), 29.5 (C₁₄), 23.1 (C₃); HRMS(ESI-TOF): calcd. for C₁₆H₂₂OH⁺: 231.1749. Found: 231.1741 (MH⁺), 253.1556 (MNa⁺). This is consistent with literature data.⁵³

1-(2-(3,3-Dimethylbutyl)naphthalene-1-yl)ethanone **5.33**



According to representative procedure 7.5.3, the product was purified by silica column chromatography (eluent; petroleum ether b. p. 40-60 °C/Et₂O, 16:1, R_f = 0.22, det: KMnO₄) and isolated as a brown oil (252 mg, 99%). IR: $\nu_{\max}/\text{cm}^{-1}$ (neat) 2953, 1699, 1467, 1364, 1350, 1205, 955, 818, 741; ¹H NMR: (CDCl₃, 300 MHz) δ = 7.72-7.87 (2H, m, H₆ & H₁₁), 7.56-7.63 (1H, m, H₈), 7.42-7.53 (2H, m, H₉ & H₁₀), 7.32 (1H, d, *J* = 8.40 Hz, H₅), 2.65 (3H, s, H₂), 2.60-2.66 (2H, m, H₁₃), 1.51-1.57 (2H, m, H₁₄), 0.98 (9H, s, H₁₆); ¹³C NMR: (CDCl₃, 75.4 MHz) δ = 208.2 (C₁), 138.5 (C₄), 135.6 (C₆), 131.9 (C₇), 129.1 (C₁₂), 129.0 (C₈), 128.4 (C₁₀), 127.8 (C₃), 126.9 (C₅), 125.6 (C₁₁), 124.1 (C₉), 46.6 (C₁₄), 33.5 (C₂), 30.8 (C₁₅), 29.3 (C₁₆), 29.1 (C₁₃); HRMS(ESI-TOF): calcd. for C₁₈H₂₂OH⁺: 255.1749. Found: 255.1733 (MH⁺), 277.1552 (MNa⁺); CHN: *Anal. Calc.* for C₁₈H₂₂O: C, 84.99%, H, 8.72%; Found: C, 84.90%, H, 8.72%.

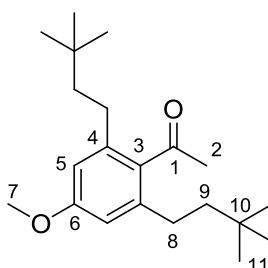
1-(3-(3,3-Dimethylbutyl)thiophen-2-yl)ethanone **5.34**



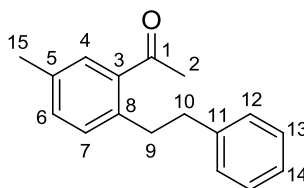
According to representative procedure 7.5.3, the product was purified by silica column chromatography (eluent; petroleum ether b. p. 40-60 °C/Et₂O, 20:1, R_f = 0.25, det: KMnO₄) and isolated as a brown oil (160 mg, 76%). IR: $\nu_{\max}/\text{cm}^{-1}$ (neat)

2953, 1664, 1521, 1409 1380, 1264, 1242, 846, 731; ^1H NMR: (CDCl_3 , 300 MHz) δ = 7.40 (1H, d, J = 5.10 Hz, H_{10}), 6.99 (1H, d, J = 5.10 Hz, H_9), 2.95-3.01 (2H, m, H_1), 2.54 (3H, s, H_5), 1.44-1.49 (2H, m, H_2), 0.98 (9H, s, H_4); ^{13}C NMR: (CDCl_3 , 75.4 MHz) δ = 191.0 (C_6), 151.2 (C_7), 135.5 (C_8), 131.7 (C_{10}), 129.9 (C_9), 44.7 (C_2), 30.7 (C_3), 29.9 (C_5), 29.4 (C_4), 25.9 (C_1); HRMS(ESI-TOF): calcd. for $\text{C}_{12}\text{H}_{18}\text{OS}^+$: 211.1157. Found: 211.1157 (MH^+), 233.0969 (MNa^+); CHN: *Anal. Calc.* for $\text{C}_{12}\text{H}_{18}\text{OS}$: C, 68.52%, H, 8.63%; Found: C, 68.40%, H, 8.53%.

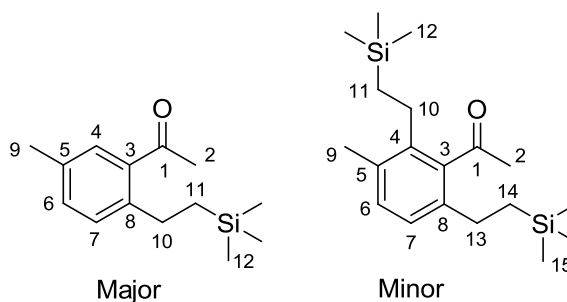
1-(2,6-Bis(3,3-dimethylbutyl)-4-methoxyphenyl)ethanone **5.35**



According to representative procedure 7.5.3, the product was purified by silica column chromatography (eluent; petroleum ether b. p. 40-60 °C/ Et_2O , 20:1, R_f = 0.21, det: KMnO_4) and isolated as a brown oil (271 mg, 85%). IR: $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 2953, 1694, 1601, 1466, 1364, 1320, 1154, 1079, 966; ^1H NMR: (CDCl_3 , 300 MHz) δ = 6.56 (2H, s, H_5), 3.80 (3H, s, H_7), 2.48 (3H, s, H_2), 2.40-2.45 (4H, m, H_8), 1.43-1.48 (4H, m, H_9), 0.93 (18H, s, H_{11}); ^{13}C NMR: (CDCl_3 , 75.4 MHz) δ = 208.1 (C_1), 159.8 (C_6), 140.2 (C_4), 135.1 (C_3), 112.3 (C_5), 55.3 (C_7), 46.5 (C_9), 33.5 (C_2), 30.7 (C_{10}), 29.3 (C_{11}), 28.9 (C_8); HRMS(ESI-TOF): calcd. for $\text{C}_{21}\text{H}_{34}\text{O}_2\text{H}^+$: 319.2637. Found: 319.2632 (MH^+), 341.2441 (MNa^+); CHN: *Anal. Calc.* for $\text{C}_{21}\text{H}_{34}\text{O}_2$: C, 79.19%, H, 10.76%; Found: C, 79.09%, H, 10.67%.

1-(5-Methyl-2-phenethylphenyl)ethanone **5.37**

According to representative procedure 7.5.3, the product was purified by silica column chromatography (eluent; petroleum ether b. p. 40-60 °C/Et₂O, 14:1, R_f = 0.20, det: KMnO₄) and isolated as a brown oil (160 mg, 67%). IR: $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3026, 2923, 1681, 1495, 1354, 1272, 1187, 750, 698; ¹H NMR: (CDCl₃, 300 MHz) δ = 7.46 (1H, s, H₄), 7.11-7.30 (7H, m, arom. H), 3.08-3.13 (2H, m, H₉), 2.83-2.88 (2H, m, H₁₀), 2.52 (3H, s, H₂), 2.38 (3H, s, H₁₅); ¹³C NMR: (CDCl₃, 75.4 MHz) δ = 202.2 (C₁), 142.2 (C₁₁), 139.0 (C₃), 138.0 (C₈), 135.6 (C₅), 132.3 (C₆), 131.5 (C₇), 129.9 (C₁₄), 128.8 (C₁₃), 128.4 (C₁₂), 125.9 (C₄), 38.4 (C₉), 36.1 (C₁₀), 29.8 (C₂), 21.1 (C₁₅); HRMS(ESI-TOF): calcd. for C₁₇H₁₈O⁺: 239.1436. Found: 239.1436 (MH⁺), 261.1254 (MNa⁺); CHN: *Anal. Calc.* for C₁₇H₁₈O: C, 85.67%, H, 7.61%; Found: C, 85.77%, H, 7.62%.

1-(5-(Methyl-2-(trimethylsilyl)ethyl)phenyl)ethanone **5.38**

According to representative procedure 7.5.3, the product was purified by silica column chromatography (eluent; petroleum ether b. p. 40-60 °C/Et₂O, 24:1, R_f = 0.37 & 0.23, det: KMnO₄) and isolated as a brown oil (151 mg, 59%). IR: $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 2953, 1685, 1415, 1247, 860, 827, 691; ¹H NMR: (CDCl₃, 300 MHz) δ = Major 7.41 (1H, s, H₄), 7.20 (1H, dd, *J* = 7.80 1.50 Hz, H₆), 7.15 (1H, d, *J* = 7.80 Hz, H₇), 2.76-2.82 (2H, m, H₁₀), 2.56 (3H, s, H₂), 2.36 (3H, s, H₉), 0.76-0.82 (2H, m, H₁₁), 0.03 (9H, s, H₁₂); Minor 7.07 (1H, d, *J* = 7.80 Hz, H₆), 6.97 (1H, d, *J* = 7.80 Hz, H₇), 2.47 (3H, s, H₂), 2.38-2.45 (4H, m, H₁₀ & H₁₃), 2.27 (3H, s, H₉), 0.68-0.83 (4H, m, H₁₁ & H₁₄), 0.01 (18H, s, H₁₂ & H₁₅); ¹³C NMR: (CDCl₃, 75.4 MHz) δ = Major 202.4 (C₁),

142.9 (C₃), 137.5 (C₈), 135.0 (C₅), 132.3 (C₆), 130.5 (C₇), 129.8 (C₄), 30.0 (C₂), 28.0 (C₁₀), 21.0 (C₉), 19.7 (C₁₁), -1.65 (C₁₂); Minor 208.7 (C₁), 141.5 (C₄), 138.0 (C₅), 137.6 (C₆), 133.3 (C₃), 130.9 (C₇), 126.0 (C₈), 33.4 (C₂), 27.2 (C₁₃), 24.9 (C₁₀), 19.5 (C₉), 18.9 (C₁₁), 18.4 (C₁₄), -1.76 (C₁₅), -1.87 (C₂); HRMS(ESI-TOF): calcd. for C₁₄H₂₂OSiNa⁺: 257.1338. Found: 257.1337 (MNa⁺); HRMS(ESI-TOF): calcd. for C₁₉H₃₄OSi₂H⁺: 335.2221. Found: 335.2224 (MH⁺); CHN: *Anal. Calc.* for C₁₅H₂₄O₂: C, 71.73%, H, 9.46%; Found: C, 71.90%, H, 9.53%.

7.6 Experimental procedures: Chapter 6

7.6.1 Representative Procedure for the Synthesis of Vinylic Alcohols

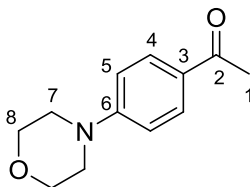
To an oven dried, nitrogen purged round bottom flask was added the aldehyde (30 mmol) and THF (100 mL) before cooling to 0 °C using an ice/water bath. Vinylmagnesium bromide solution (1.0 M in THF, 33 mL, 33 mmol) was then added dropwise. Once the addition was complete the reaction was allowed to warm to room temperature over 2 hours. NH₄Cl (sat. solution, 50 mL) and H₂O (50 mL) were added before the organic layer was separated. The aqueous layer was then extracted with EtOAc (2 x 50 mL). The combined organic phase was then dried (MgSO₄) and concentrated *in vacuo*. The crude product was then purified by silica column chromatography.

7.6.2 Representative Procedure for the Ruthenium Catalysed Tandem Isomerisation/Substitution

To an oven-dried, nitrogen purged Young's tube containing Ru(PPh₃)₃(CO)(H)₂ (110 mg, 0.12 mmol) were added 1-(4-Fluorophenyl)prop-2-en-1-ol (457 mg, 3 mmol), morpholine (0.58 mL, 6.6 mmol) and DMSO (3 mL). The reaction vessel was then sealed and heated to 115 °C for 24 hours. On completion the reaction was allowed to cool to room temperature before H₂O (20 mL) and brine (5 mL) were added. The solution was then extracted with Et₂O (3 x 25 mL). The combined organic phase was then concentrated *in vacuo*. The crude product was then purified by silica column chromatography.

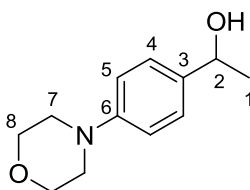
7.6.3 Synthesis of Materials for Initial Testing

1-(4-morpholinophenyl)ethanone **6.3**



4-Fluoroacetophenone (5 mL, 41 mmol) and morpholine (11.5 mL, 131 mmol) were dissolved in DMSO (100 mL) before heating to 125 °C overnight. The reaction was allowed to cool to room temperature before adding H₂O (300 mL). The precipitate was then filtered and washed with H₂O (2 x 150 mL). The crude product was then dissolved in a minimum of Et₂O before precipitating with hexane. The product (3.49g, 41%) was isolated as a yellow crystalline solid. ¹H NMR: (CDCl₃, 300 MHz) δ = 7.91 (2H, d, J = 9.00 Hz, H₄), 6.89 (2H, d, J = 8.70 Hz, H₅), 3.88 (4H, app. t, J = 4.95 Hz, H₈), 3.32 (4H, app. t, J = 4.95 Hz, H₇), 2.54 (3H, s, H₁); ¹³C NMR: (CDCl₃, 75.4 MHz) δ = 196.7 (C₂), 154.3 (C₆), 130.5 (C₄), 128.2 (C₃), 113.4 (C₅), 66.7 (C₈), 47.6 (C₇), 26.3 (C₁); HRMS(ESI-TOF): calcd. for C₁₆H₂₂O⁺: 231.1749. Found: 231.1741 (MH⁺), 253.1556 (MNa⁺). This is consistent with literature data.⁵⁴

1-(4-Morpholinophenyl)ethanol **6.4**

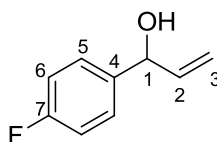


1-(4-Morpholinophenyl)ethanone (**6.3**) (2.89 g, 14 mmol) was dissolved in EtOH (100 mL) before NaBH₄ (0.76 g, 20 mmol) was added portionwise before leaving to stir overnight. H₂O (50 mL) and brine (150 mL) were added before leaving to stir for 2 hours. The solution was then transferred to a separating funnel and extracted with EtOAc (3 x 100 mL). The combined organic layers were then dried (MgSO₄) before concentrating *in vacuo*. The crude material was then dissolved in a minimum of CH₂Cl₂ before precipitating with hexane. The product (2.52 g, 87%) was isolated as a colourless crystalline solid. ¹H NMR: (CDCl₃, 300 MHz) δ = 7.30 (2H, d, J = 8.70

Hz, H₄), 6.91 (2H, d, $J = 8.40$ Hz, H₅), 4.84 (1H, q, $J = 6.60$ Hz, H₂), 3.86 (4H, app. t, $J = 4.80$ Hz, H₈), 3.13 (4H, app. t, $J = 4.95$ Hz, H₇), 1.74 (1H, br s, OH), 1.48 (3H, d, $J = 6.60$ Hz, H₁); ¹³C NMR: (CDCl₃, 75.4 MHz) $\delta = 150.8$ (C₆), 137.5 (C₃), 126.5 (C₄), 115.8 (C₅), 67.0 (C₂), 67.0 (C₈), 49.5 (C₇), 25.0 (C₁); HRMS(ESI-TOF): calcd. for C₁₂H₁₇NOH⁺: 208.1332. Found: 208.1417 (MH⁺), 230.1153 (MNa⁺). This is consistent with literature data.⁵⁵

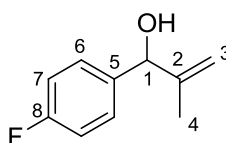
7.6.4 Synthesis of Vinylic Alcohol Starting Materials

1-(4-Fluorophenyl)prop-2-en-1-ol **6.11**



According to literature procedure 7.6.1, the product was purified by silica column chromatography (eluent; petroleum ether b. p. 40-60 °C/Et₂O, 4:1, R_f = 0.19, det: KMnO₄) and isolated as a yellow oil (10.1 g, 71%). ¹H NMR: (CDCl₃, 300 MHz) $\delta = 7.35$ (2H, dd, $J = 8.70$ 5.40 Hz, H₅), 7.04 (2H, app. t, $J = 8.70$ Hz, H₆), 5.97-6.08 (1H, m, H₂), 5.31-5.38 (1H, m, H₃), 5.19-5.23 (2H, m, H₁ & H₃) 1.80 (1H, br s, OH); ¹³C NMR: (CDCl₃, 75.4 MHz) $\delta = 162.4$ (d, $J = 245.4$ Hz, C₇), 140.2 (C₂), 138.4 (d, $J = 3.1$ Hz, C₄), 128.2 (d, $J = 8.1$ Hz, C₅), 115.5 (d, $J = 21.4$ Hz, C₆), 115.5 (C₃), 74.8 (C₁); HRMS(ESI-TOF): calcd. for C₉H₈OF⁺: 151.0559. Found: 151.0571 (M⁺). This is consistent with literature data.⁵⁶

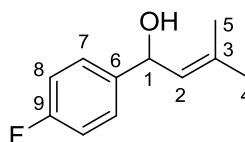
1-(4-Fluorophenyl)-2-methylprop-2-en-1-ol **6.28**



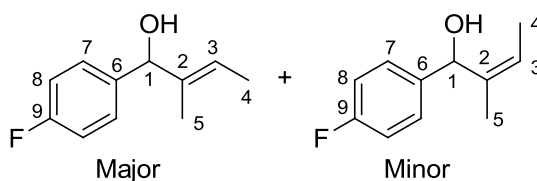
According to literature procedure 7.6.1 using *isopropenylmagnesium bromide* solution, the product was purified by silica column chromatography (eluent; petroleum ether b. p. 40-60 °C/Et₂O, 4:1, R_f = 0.19, det: KMnO₄) and isolated as a yellow oil (10.1 g, 71%). IR: ν_{max} /cm⁻¹ (neat) 3359, 1603, 1507, 1220, 1156, 1046,

903, 830; ^1H NMR: (CDCl_3 , 300 MHz) δ = 7.34 (2H, dd, J = 8.70 5.40 Hz, H_6), 7.03 (2H, app. t, J = 8.70 Hz, H_7), 5.19-5.20 (1H, m, H_1), 5.13 (1H, s, H_3), 4.95-4.97 (1H, m, H_3), 1.89 (1H, br s, OH), 1.60 (3H, s, H_4); ^{13}C NMR: (CDCl_3 , 75.4 MHz) δ = 162.4 (d, J = 246.8 Hz, C_8), 146.9 (C_2), 137.8 (d, J = 3.1 Hz, C_5), 128.3 (d, J = 8.1 Hz, C_7), 115.3 (d, J = 21.3 Hz, C_6), 111.5 (C_3), 77.3 (C_1), 18.3 (C_4); ^{19}F NMR: (CDCl_3 , 376 MHz) δ = -115.1 (tt, J = 8.6 5.6 Hz); HRMS(ESI-TOF): calcd. for $\text{C}_{10}\text{H}_{11}\text{FONa}^+$: 189.0692. Found: 189.0679 (MNa^+); CHN: *Anal. Calc.* for $\text{C}_{10}\text{H}_{11}\text{FO}$: C, 72.27%, H, 6.67%; Found: C, 72.45%, H, 6.68%.

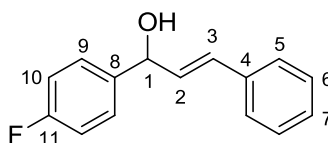
1-(4-Fluorophenyl)-3-methylbut-2-en-1-ol **6.29**



According to literature procedure 7.6.1 using 2-methyl-1-propenylmagnesium bromide solution, the product was purified by silica column chromatography (eluent; petroleum ether b. p. 40-60 °C/ Et_2O , 1:1, R_f = 0.28, det: KMnO_4) and isolated as a yellow oil (4.59 g, 85%). IR: $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3339, 2975, 1603, 1507, 1220, 1156, 816; ^1H NMR: (CDCl_3 , 300 MHz) δ = 7.35 (2H, dd, J = 8.70 5.40 Hz, H_7), 7.02 (2H, app. t, J = 8.70 Hz, H_8), 5.45 (1H, d, J = 8.70 Hz, H_2), 5.35-5.40 (1H, m, H_1), 1.80 (3H, d, J = 1.50 Hz, H_4), 1.76 (3H, d, J = 1.20 Hz, H_5); ^{13}C NMR: (CDCl_3 , 75.4 MHz) δ = 162.1 (d, J = 244.7 Hz, C_9), 140.0 (d, J = 3.0 Hz, C_6), 135.6 (C_3), 127.6 (C_2), 127.6 (d, J = 8.1 Hz, C_7), 115.3 (d, J = 21.3 Hz, C_8), 70.2 (C_1), 26.0 (C_4), 18.4 (C_5); ^{19}F NMR: (CDCl_3 , 376 MHz) δ = -114.7 (tt, J = 8.6 5.6 Hz); HRMS(ESI-TOF): calcd. for $\text{C}_{11}\text{H}_{12}\text{FO}^-$: 179.0872. Found: 179.0860 (M^-); CHN: *Anal. Calc.* for $\text{C}_{11}\text{H}_{13}\text{FO}$: C, 73.31%, H, 7.27%; Found: C, 73.39%, H, 7.40%.

1-(4-Fluorophenyl)-2-methylbut-2-en-1-ol **6.30**

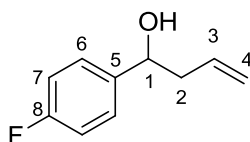
According to literature procedure 7.6.1 using 1-methyl-1-propenylmagnesium bromide solution, the product was purified by silica column chromatography (eluent; cyclohexane/EtOAc, 0-100% over 60 min, det: KMnO_4) and isolated as a yellow oil (3.46 g, 64%). IR: $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3345, 2921, 1602, 1506, 1221, 1155, 1011, 839; ^1H NMR: (CDCl_3 , 300 MHz) δ = Major 7.296-7.35 (2H, m, H_7), 6.99-7.05 (2H, m, H_8), 5.78 (1H, s, H_1), 5.47 (1H, q, J = 6.90 Hz, H_3), 1.79 (3H, d, J = 6.90 Hz, H_4), 1.56 (3H, s, H_5); Minor 7.296-7.35 (2H, m, H_7), 6.99-7.05 (2H, m, H_8), 5.71 (1H, q, J = 6.60 Hz, H_3), 5.12 (1H, s, H_1), 1.66 (3H, d, J = 6.60 Hz, H_4), 1.47 (3H, s, H_5); ^{13}C NMR: (CDCl_3 , 75.4 MHz) δ = Major 162.0 (d, J = 244.4 Hz, C_9), 138.3 (d, J = 3.0 Hz, C_6), 137.1 (C_2), 127.2 (d, J = 7.9 Hz, C_7), 122.8 (C_3), 115.1 (d, J = 21.3 Hz, C_8), 70.1 (C_1), 17.4 (C_4), 13.4 (C_5); Minor 162.2 (d, J = 244.6 Hz, C_9), 138.2 (d, J = 3.0 Hz, C_6), 137.6 (C_2), 127.9 (d, J = 8.0 Hz, C_7), 121.7 (C_3), 115.1 (d, J = 21.3 Hz, C_8), 78.9 (C_1), 13.3 (C_5), 11.7 (C_4); ^{19}F NMR: (CDCl_3 , 376 MHz) δ = Major -116.3 (tt, J = 8.6 5.6 1.1 Hz); Minor -115.9 (dt, J = 8.6 5.6 0.8 Hz); HRMS(ESI-TOF): calcd. for $\text{C}_{11}\text{H}_{13}\text{FONa}^+$: 203.0848. Found: 203.0843 (MNa^+); CHN: *Anal. Calc.* for $\text{C}_{11}\text{H}_{13}\text{FO}$: C, 73.31%, H, 7.27%; Found: C, 73.30%, H, 7.30%.

(E)-1-(4-Fluorophenyl)-3-phenylprop-2-en-1-ol **6.31**

(E)-1-(4-Fluorophenyl)-3-phenylprop-2-en-1-one (4.37 g, 19 mmol) was dissolved in MeOH (50 mL). NaBH_4 (0.87 g, 23 mmol) was added portionwise before leaving to stir at room temperature overnight. H_2O (50 mL) and brine (50 mL) were added before the organic layer was separated and the aqueous layer extracted with EtOAc (2 x 50 mL). The combined organic phase was then dried (MgSO_4) and concentrated *in vacuo*. The crude material was then purified by silica column chromatography (eluent; petroleum ether b. p. 40-60 $^\circ\text{C}$ /Et $_2$ O, 4:1, R_f = 0.20) and isolated as a

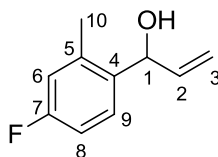
colourless oil (3.73 g, 86%). ^1H NMR: (CDCl_3 , 300 MHz) δ = 7.22-7.44 (7H, m, arom. H), 7.06 (2H, app. t, J = 8.70 Hz, H_8), 6.68 (1H, d, J = 15.60 Hz, H_3), 6.35 (1H, dd, J = 15.90 6.60 Hz, H_2), 5.38 (1H, d, J = 6.60 Hz, H_1), 2.01 (1H, d, J = 2.40 Hz, OH); ^{13}C NMR: (CDCl_3 , 75.4 MHz) δ = 162.5 (d, J = 245.7 Hz, C_{11}), 138.6 (d, J = 3.1 Hz, C_8), 136.5 (C_4), 131.4 (C_3), 130.9 (C_7), 128.8 (C_6), 128.2 (d, J = 8.1 Hz, C_9), 128.1 (C_2), 126.8 (C_5), 115.6 (d, J = 21.4 Hz, C_{10}), 74.6 (C_1); HRMS(ESI-TOF): calcd. for $\text{C}_{15}\text{H}_{12}\text{FONa}^+$: 227.0872. Found: 227.0866 (M^+). This is consistent with literature data.⁵⁷

1-(4-Fluorophenyl)but-3-en-1-ol **6.32**



According to literature procedure 7.6.1 using allylmagnesium bromide solution, the product was then purified by Kugelrohr distillation and isolated as a colourless oil (3.98 g, 80%). ^1H NMR: (CDCl_3 , 300 MHz) δ = 7.33 (2H, dd, J = 8.70 5.40 Hz, H_6), 7.04 (2H, app. t, J = 8.70 Hz, H_7), 5.73-5.86 (1H, m, H_3), 5.14-5.20 (2H, m, H_4), 4.73 (1H, dd, J = 7.20 5.70 Hz, H_1), 2.46-2.52 (2H, m, H_2), 2.00 (1H, d, J = 1.50 Hz, OH); ^{13}C NMR: (CDCl_3 , 75.4 MHz) δ = 162.3 (d, J = 245.0 Hz, C_8), 139.7 (d, J = 3.1 Hz, C_5), 134.3 (C_3), 127.6 (d, J = 8.1 Hz, C_6), 118.8 (C_4), 115.3 (d, J = 21.3 Hz, C_7), 72.8 (C_1), 44.1 (C_2); HRMS(ESI-TOF): calcd. for $\text{C}_{10}\text{H}_{11}\text{FONa}^+$: 189.0692. Found: 189.0691 (MNa^+). This is consistent with literature data.⁵⁸

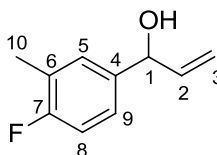
1-(4-Fluoro-2-methylphenyl)prop-2-en-1-ol **6.38**



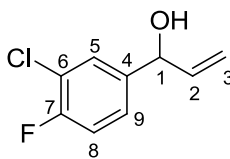
According to literature procedure 7.6.1, the product was purified by Kugelrohr distillation and isolated as a colourless oil (4.21 g, 84%). IR: $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3316, 2981, 1614, 1590, 1495, 1237, 987, 955, 924, 861, 805; ^1H NMR: (CDCl_3 , 300 MHz) δ = 7.41 (1H, dd, J = 8.40 6.00 Hz, H_9), 6.92 (1H, dd, J = 8.40 2.70 Hz, H_8), 6.86

(1H, dd, $J = 9.30$ 2.70 Hz, H_6), 6.01 (1H, ddd, $J = 17.10$ 10.20 5.70 Hz, H_2), 5.38 (1H, dd, $J = 5.10$ 4.20 Hz, H_1), 5.31 (1H, dt, $J = 17.10$ 1.20 Hz, H_3), 5.22 (1H, dt, $J = 10.20$ 1.20 Hz, H_3), 2.35 (3H, s, H_{10}), 1.79 (1H, d, $J = 3.90$ Hz, OH); ^{13}C NMR: (CDCl_3 , 75.4 MHz) $\delta = 162.1$ (d, $J = 245.1$ Hz, H_7), 139.4 (C_2), 138.0 (d, $J = 7.8$ Hz, C_5), 136.3 (d, $J = 3.1$ Hz, C_4), 127.8 (d, $J = 8.5$ Hz, C_9), 117.2 (d, $J = 21.0$ Hz, C_6), 115.5 (C_3), 113.0 (d, $J = 20.8$ Hz, C_8), 71.7 (C_1), 19.3 (d, $J = 1.4$ Hz, C_{10}); ^{19}F NMR: (CDCl_3 , 376 MHz) $\delta = -115.8$ (ddd, $J = 9.8$ 8.6 6.0 Hz); HRMS(ESI-TOF): calcd. for $\text{C}_{11}\text{H}_{11}\text{FONa}^+$: 189.0692. Found: 189.0683 (MNa^+); CHN: *Anal. Calc.* for $\text{C}_{10}\text{H}_{11}\text{FO}$: C, 72.27%, H, 6.67%; Found: C, 72.45%, H, 6.69%.

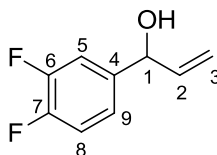
1-(4-Fluoro-3-methylphenyl)prop-2-en-1-ol **6.39**



According to literature procedure 7.6.1, the product was purified by silica column chromatography (eluent; petroleum ether b. p. 40-60 °C/ Et_2O , 3:1, $R_f = 0.23$, det: KMnO_4) and isolated as a yellow oil (4.58 g, 77%). IR: $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3344, 2928, 1499, 1247, 1206, 1115, 987, 925, 822, 756; ^1H NMR: (CDCl_3 , 300 MHz) $\delta = 7.12$ -7.21 (2H, m, H_5 & H_9), 6.98 (1H, dd, $J = 9.30$ 8.70 Hz, H_8), 6.03 (1H, ddd, $J = 17.10$ 10.20 6.00 Hz, H_2), 5.34 (1H, dt, $J = 17.10$ 1.20 Hz, H_3), 5.20 (1H, dt, $J = 10.20$ 1.20 Hz, H_3), 5.16 (1H, m, H_1), 2.28 (3H, d, $J = 1.80$ Hz, H_{10}), 1.87 (1H, d, $J = 3.60$ Hz, OH); ^{13}C NMR: (CDCl_3 , 75.4 MHz) $\delta = 161.0$ (d, $J = 244.4$ Hz, C_7), 140.3 (C_2), 138.1 (d, $J = 3.5$ Hz, C_4), 129.6 (d, $J = 5.3$ Hz, C_5), 125.4 (d, $J = 8.1$ Hz, C_9), 125.1 (d, $J = 17.4$ Hz, C_6), 115.3 (C_3), 115.1 (d, $J = 22.6$ Hz, C_8), 74.9 (C_1), 14.7 (d, $J = 3.5$ Hz, C_{10}); ^{19}F NMR: (CDCl_3 , 376 MHz) $\delta = -119.2$ (m); HRMS(ESI-TOF): calcd. for $\text{C}_{10}\text{H}_{10}\text{FO}$: 165.0716. Found: 165.0705 (M); CHN: *Anal. Calc.* for $\text{C}_{10}\text{H}_{11}\text{FO}$: C, 72.27%, H, 6.67%; Found: C, 72.40%, H, 6.73%.

1-(3-Chloro-4-fluorophenyl)prop-2-en-1-ol **6.40**

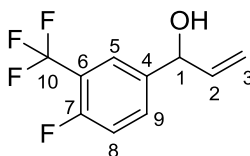
According to literature procedure 7.6.1, the product was purified by silica column chromatography (eluent; petroleum ether b. p. 40-60 °C/Et₂O, 3:1, R_f = 0.21, det: KMnO₄) and isolated as a yellow oil (2.98 g, 50%). IR: $\nu_{\max}/\text{cm}^{-1}$ (neat) 3339, 1497, 1407, 1248, 1059, 987, 930, 823, 713, 696; ¹H NMR: (CDCl₃, 300 MHz) δ = 7.44 (1H, dd, J = 7.20 1.20 Hz, H₅), 7.24 (1H, dddd, J = 8.4 4.2 2.1 0.3 Hz, H₉), 7.12 (1H, app. t, J = 8.70 Hz, H₈), 5.98 (1H, ddd, J = 16.50 10.20 6.60 Hz, H₂), 5.36 (1H, dt, J = 17.10 1.20 Hz, H₃), 5.24 (1H, dt, J = 10.20 1.20 Hz, H₃), 5.18 (1H, app. t, J = 4.20 Hz, H₁), 1.95 (1H, d, J = 3.60 Hz, OH); ¹³C NMR: (CDCl₃, 75.4 MHz) δ = 157.6 (d, J = 248.3 Hz, C₇), 139.7 (C₂), 139.6 (d, J = 3.8 Hz, C₄), 128.7 (C₅), 126.2 (d, J = 7.2 Hz, C₉), 121.1 (d, J = 17.9 Hz, C₆), 116.7 (d, J = 21.1 Hz, C₈), 116.2 (C₃), 74.3 (C₁); ¹⁹F NMR: (CDCl₃, 376 MHz) δ = -117.2 (dddd, J = 9.0 7.1 4.5 0.8 Hz); HRMS(ESI-TOF): calcd. for C₉H₇ClFO: 185.0169. Found: 185.0157 (M⁺); CHN: *Anal. Calc.* for C₉H₈ClFO: C, 57.93%, H, 4.32%; Found: C, 57.90%, H, 4.36%.

1-(3,4-Difluorophenyl)prop-2-en-1-ol **6.41**

According to literature procedure 7.6.1, the product was purified by silica column chromatography (eluent; petroleum ether b. p. 40-60 °C/Et₂O, 4:1, R_f = 0.20, det: KMnO₄) and isolated as a yellow oil (4.19 g, 70%). IR: $\nu_{\max}/\text{cm}^{-1}$ (neat) 3338, 1610, 1514, 1432, 1278, 1208, 1111, 988, 930, 875, 822, 770, 760; ¹H NMR: (CDCl₃, 300 MHz) δ = 7.06-7.25 (3H, m, arom. H), 5.98 (1H, ddd, J = 17.10 10.20 6.00 Hz, H₂), 5.36 (1H, dt, J = 17.10 1.20 Hz, H₃), 5.24 (1H, dt, J = 10.20 1.20 Hz, H₃), 5.17 (1H, d, J = 6.00 Hz, H₁), 1.79 (1H, br s, OH); ¹³C NMR: (CDCl₃, 75.4 MHz) δ = 150.4 (dd, J = 247.8 12.7 Hz, C₆), 149.8 (dd, J = 247.4 12.7 Hz, C₇), 139.6 (C₂), 139.6 (d, J = 8.6 Hz, C₄), 122.4 (dd, J = 6.4 3.6 Hz, C₉), 117.2 (d, J = 17.3 Hz, C₈), 116.2 (C₃), 115.4 (d, J = 17.8 Hz, C₅), 74.3 (d, J = 1.3 Hz, C₁); ¹⁹F NMR: (CDCl₃, 376 MHz) δ =

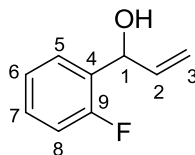
-137.5 (m), -139.6 (m); HRMS(ESI-TOF): calcd. for $C_9H_7F_2O^-$: 169.0465. Found: 169.0476 (M^-); CHN: *Anal. Calc.* for $C_9H_8F_2O$: C, 63.53%, H, 4.74%; Found: C, 63.40%, H, 4.70%.

1-(4-Fluoro-3-(trifluoromethyl)phenyl)prop-2-en-1-ol **6.42**



According to literature procedure 7.6.1, the product was purified by silica column chromatography (eluent; petroleum ether b. p. 40-60 °C/Et₂O, 4:1, R_f = 0.21, det: KMnO₄) and isolated as a yellow oil (4.53 g, 79%). IR: $\nu_{\max}/\text{cm}^{-1}$ (neat) 3343, 1624, 1505, 1435, 1322, 1240, 1123, 1056, 988, 933, 833, 679; ¹H NMR: (CDCl₃, 300 MHz) δ = 7.63 (1H, dd, J = 6.90 2.10 Hz, H₅), 7.56 (1H, ddd, J = 8.40 4.80 2.40 Hz, H₉), 7.18 (1H, app. t, J = 9.30 Hz, H₈), 6.00 (1H, ddd, J = 17.10 10.20 6.30 Hz, H₂), 5.38 (1H, dt, J = 17.10 1.20 Hz, H₃), 5.27 (1H, dt, J = 10.20 1.20 Hz, H₃), 5.24 (1H, d, J = 6.30 Hz, H₁), 1.80 (1H, br s, OH); ¹³C NMR: (CDCl₃, 75.4 MHz) δ = 159.3 (dd, J = 256.7 2.1 Hz, C₇), 139.6 (C₂), 138.8 (d, J = 3.7 Hz, C₄), 125.2 (qd, J = 4.6 1.7 Hz, C₉), 124.5 (C₅), 122.7 (q, J = 272.0 Hz, C₁₀), 118.5 (dd, J = 32.9 12.6 Hz, C₆), 117.1 (d, J = 20.7 Hz, C₈), 116.6 (C₃), 74.4 (C₁); ¹⁹F NMR: (CDCl₃, 376 MHz) δ = -61.5 (dd, J = 12.8 0.8 Hz), -116.4 (m); HRMS(ESI-TOF): calcd. for $C_{10}H_7F_4O^-$: 219.0433. Found: 219.0429 (M^-); CHN: *Anal. Calc.* for $C_{10}H_8F_4O$: C, 54.55%, H, 3.66%; Found: C, 54.50%, H, 3.68%.

1-(2-Fluorophenyl)prop-2-en-1-ol **6.43**

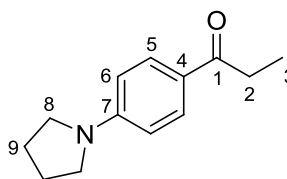


According to literature procedure 7.6.1, the product was purified by silica column chromatography (eluent; petroleum ether b. p. 40-60 °C/Et₂O, 4:1, R_f = 0.16, det: KMnO₄) and isolated as a yellow oil (3.26 g, 71%). ¹H NMR: (CDCl₃, 300 MHz) δ = 7.45 (1H, td, J = 7.50 1.80 Hz, H₇), 7.24-7.31 (1H, m, H₈), 7.16 (1H, td, J = 7.50 1.20

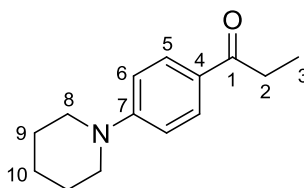
Hz, H₅), 7.04 (1H, ddd, $J = 10.50$ 8.10 1.20 Hz, H₆), 6.08 (1H, dddd, $J = 17.10$ 10.50 5.70 0.90 Hz, H₂), 5.53 (1H, app. t, $J = 5.10$ Hz, H₁), 5.36 (1H, dq, $J = 17.10$ 1.20 Hz, H₃), 5.22 (1H, dt, $J = 10.20$ 1.20 Hz, H₃), 2.01 (1H, dd, $J = 4.80$ 0.90 Hz, OH); ¹³C NMR: (CDCl₃, 75.4 MHz) $\delta = 160.2$ (d, $J = 246.1$ Hz, C₉), 139.0 (d, $J = 0.5$ Hz, C₂), 129.8 (d, $J = 13.2$ Hz, C₄), 129.4 (d, $J = 8.3$ Hz, C₇), 127.8 (d, $J = 4.2$ Hz, C₅), 124.5 (d, $J = 3.5$ Hz, C₆), 115.6 (d, $J = 21.6$ Hz, C₈), 115.5 (C₃), 69.4 (d, $J = 3.1$ Hz, C₁); HRMS(ESI-TOF): calcd. for C₉H₈FO⁻: 151.0559. Found: 151.0570 (M⁻). This is consistent with literature data.⁵⁹

7.6.5 Ruthenium Catalysed Isomerisation of 4-Fluoro Vinylic Alcohols & Nucleophilic Substitution

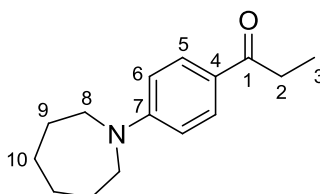
1-(4-(Pyrrolidin-1-yl)phenyl)propan-1-one **6.23**



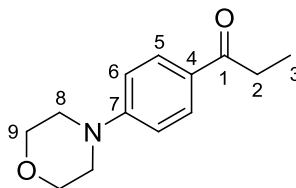
According to literature procedure 7.6.2, the product was purified by silica column chromatography (eluent; hexanes/EtOAc, 3:2, $R_f = 0.43$, det: KMnO₄) and isolated as a yellow crystalline solid (470 mg, 77%). m. p. = 135-137 °C; IR: $\nu_{\max}/\text{cm}^{-1}$ (neat) 2850, 1657, 1592, 1349, 1181, 1161, 798; ¹H NMR: (CDCl₃, 300 MHz) $\delta = 7.88$ (2H, d, $J = 9.00$ Hz, H₅), 6.52 (2H, d, $J = 9.00$ Hz, H₆), 3.34-3.39 (4H, m, H₈), 2.90 (2H, q, $J = 7.20$ Hz, H₂), 2.01-2.06 (4H, m, H₉), 1.21 (3H, t, $J = 7.20$ Hz, H₃); ¹³C NMR: (CDCl₃, 75.4 MHz) $\delta = 199.2$ (C₁), 151.0 (C₇), 130.4 (C₅), 124.6 (C₄), 110.8 (C₆), 47.7 (C₈), 31.0 (C₂), 25.5 (C₉), 9.02 (C₃); HRMS(ESI-TOF): calcd. for C₁₃H₁₇NOH⁺: 204.1388. Found: 204.1384 (MH⁺), 226.1195 (MNa⁺); CHN: *Anal. Calc.* for C₁₃H₁₇NO: C, 76.81%, H, 8.43%, N, 6.89%; Found: C, 76.80%, H, 8.36%, N, 6.69%.

1-(4-(Piperidin-1-yl)phenyl)propan-1-one **6.24**

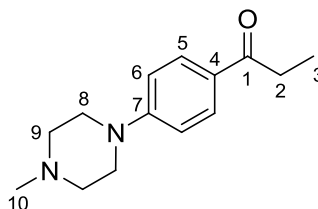
According to literature procedure 7.6.2, the product was purified by silica column chromatography (eluent; hexanes/EtOAc, 4:1, $R_f = 0.35$, det: KMnO_4) and isolated as a yellow crystalline solid (567 mg, 87%). m. p. = 85-87 °C; IR: $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 2940, 2836, 1662, 1593, 1350, 1222, 1192, 1124, 796; ^1H NMR: (CDCl_3 , 300 MHz) $\delta = 7.87$ (2H, d, $J = 9.00$ Hz, H_5), 6.85 (2H, d, $J = 9.00$ Hz, H_6), 3.33-3.36 (4H, m, H_8), 2.91 (2H, q, $J = 7.20$ Hz, H_2), 1.66-1.70 (6H, m, H_9 & H_{10}), 1.20 (3H, t, $J = 7.20$ Hz, H_3); ^{13}C NMR: (CDCl_3 , 75.4 MHz) $\delta = 199.3$ (C_1), 154.5 (C_7), 130.2 (C_5), 126.5 (C_4), 113.5 (C_6), 48.8 (C_8), 31.2 (C_2), 25.5 (C_9), 24.5 (C_{10}), 8.9 (C_3); HRMS(ESI-TOF): calcd. for $\text{C}_{14}\text{H}_{19}\text{NONa}^+$: 240.1364. Found: 240.1362 (MNa^+); CHN: *Anal. Calc.* for $\text{C}_{14}\text{H}_{19}\text{NO}$: C, 77.38%, H, 8.81%, N, 6.45%; Found: C, 77.36%, H, 8.84%, N, 6.60%.

1-(4-(Azepan-1-yl)phenyl)propan-1-one **6.25**

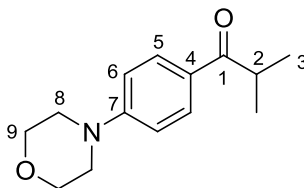
According to literature procedure 7.6.2, the product was purified by silica column chromatography (eluent; hexanes/EtOAc, 5:1, $R_f = 0.27$, det: KMnO_4) and isolated as a yellow crystalline solid (562 mg, 81%). m. p. = 85-87 °C; IR: $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 2919, 1657, 1589, 1520, 1405, 1348, 1184, 796; ^1H NMR: (CDCl_3 , 300 MHz) $\delta = 7.86$ (2H, d, $J = 9.30$ Hz, H_5), 6.65 (2H, d, $J = 9.30$ Hz, H_6), 3.52 (4H, t, $J = 6.00$ Hz, H_8), 2.89 (2H, q, $J = 7.20$ Hz, H_2), 1.79-1.82 (4H, m, H_9), 1.53-1.57 (4H, m, H_{10}), 1.20 (3H, t, $J = 7.20$ Hz, H_3); ^{13}C NMR: (CDCl_3 , 75.4 MHz) $\delta = 199.1$ (C_1), 152.3 (C_7), 130.6 (C_5), 124.5 (C_4), 110.2 (C_6), 49.5 (C_8), 31.0 (C_2), 27.5 (C_9), 27.0 (C_{10}), 9.0 (C_3); HRMS(ESI-TOF): calcd. for $\text{C}_{15}\text{H}_{21}\text{NOH}^+$: 232.1701. Found: 232.1742 (MH^+), 254.1505 (MNa^+); CHN: *Anal. Calc.* for $\text{C}_{14}\text{H}_{19}\text{NO}$: C, 77.88%, H, 9.15%, N, 6.05%; Found: C, 77.68%, H, 8.96%, N, 5.93%.

1-(4-Morpholinophenyl)propan-1-one **6.26**

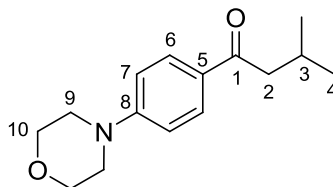
According to literature procedure 7.6.2, the product was purified by silica column chromatography (eluent; hexanes/EtOAc, 1:1, $R_f = 0.36$, det: KMnO_4) and isolated as a yellow crystalline solid (566 mg, 86%). m. p. = 77-79 °C; IR: $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 2972, 2858, 1665, 1598, 1227, 1190, 1122, 923, 795; ^1H NMR: (CDCl_3 , 300 MHz) $\delta = 7.91$ (2H, d, $J = 9.00$ Hz, H_5), 6.87 (2H, d, $J = 9.00$ Hz, H_6), 3.86 (4H, app. t, $J = 4.95$ Hz, H_9), 3.30 (4H, app. t, $J = 4.95$ Hz, H_8), 2.93 (2H, q, $J = 7.20$ Hz, H_2), 1.21 (3H, t, $J = 7.20$ Hz, H_3); ^{13}C NMR: (CDCl_3 , 75.4 MHz) $\delta = 199.4$ (C_1), 154.2 (C_7), 130.1 (C_5), 128.0 (C_4), 113.5 (C_6), 66.7 (C_9), 47.7 (C_8), 31.3 (C_2), 8.7 (C_3); HRMS(ESI-TOF): calcd. for $\text{C}_{13}\text{H}_{17}\text{NO}_2\text{H}^+$: 220.1338. Found: 220.1321 (MH^+), 242.1140 (MNa^+); CHN: *Anal. Calc.* for $\text{C}_{13}\text{H}_{17}\text{NO}_2$: C, 71.21%, H, 7.81%, N, 6.39%; Found: C, 71.02%, H, 7.79%, N, 6.27%.

1-(4-(4-Methylpiperazin-1-yl)phenyl)propan-1-one **6.27**

According to literature procedure 7.6.2, the product was purified by silica column chromatography (eluent; $\text{CH}_2\text{Cl}_2/\text{MeOH}$, 92:8, $R_f = 0.33$, det: KMnO_4) and isolated as a yellow crystalline solid (495 mg, 71%). m. p. = 105-107 °C; IR: $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 2849, 2858, 1668, 1594, 1348, 1292, 1223, 1190, 997, 919, 798; ^1H NMR: (CDCl_3 , 300 MHz) $\delta = 7.89$ (2H, d, $J = 9.00$ Hz, H_5), 6.87 (2H, d, $J = 9.00$ Hz, H_6), 3.36 (4H, app. t, $J = 5.10$ Hz, H_8), 2.92 (2H, q, $J = 7.20$ Hz, H_2), 2.56 (4H, app. t, $J = 5.10$ Hz, H_9), 2.35 (3H, s, H_{10}), 1.20 (3H, t, $J = 7.20$ Hz, H_3); ^{13}C NMR: (CDCl_3 , 75.4 MHz) $\delta = 199.4$ (C_1), 154.1 (C_7), 130.1 (C_5), 127.4 (C_4), 113.6 (C_6), 54.9 (C_9), 47.4 (C_8), 46.3 (C_{10}), 31.3 (C_2), 8.8 (C_3); HRMS(ESI-TOF): calcd. for $\text{C}_{14}\text{H}_{20}\text{N}_2\text{OH}^+$: 233.1648. Found: 233.1723 (MH^+); CHN: *Anal. Calc.* for $\text{C}_{14}\text{H}_{20}\text{N}_2\text{O}$: C, 72.38%, H, 8.68%, N, 12.06%; Found: C, 72.19%, H, 8.61%, N, 12.00%.

2-Methyl-1-(4-morpholinophenyl)propan-1-one **6.33**

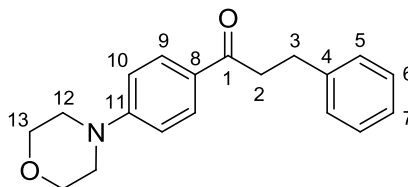
According to literature procedure 7.6.2 run for 48 hours with 5 mol% catalyst, the product was purified by silica column chromatography (eluent; hexanes/EtOAc, 2:1, $R_f = 0.33$, det: KMnO_4) and isolated as a yellow crystalline solid (364 mg, 52%). m. p. = 69-71 °C; IR: $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 2963, 2858, 1662, 1597, 1222, 1207, 1112, 923, 844, 645; ^1H NMR: (CDCl_3 , 300 MHz) $\delta = 7.91$ (2H, d, $J = 9.00$ Hz, H_5), 6.87 (2H, d, $J = 9.00$ Hz, H_6), 3.85 (4H, app. t, $J = 4.95$ Hz, H_9), 3.50 (1H, sept, $J = 6.90$ Hz, H_2), 3.29 (4H, app. t, $J = 4.95$ Hz, H_8), 1.19 (6H, d, $J = 6.90$ Hz, H_3); ^{13}C NMR: (CDCl_3 , 75.4 MHz) $\delta = 202.9$ (C_1), 154.2 (C_7), 130.4 (C_5), 127.1 (C_4), 113.5 (C_6), 66.7 (C_9), 47.7 (C_8), 34.8 (C_2), 19.5 (C_3); HRMS(ESI-TOF): calcd. for $\text{C}_{14}\text{H}_{19}\text{NO}_2\text{H}^+$: 234.1494. Found: 234.1488 (MH^+), 256.1292 (MNa^+); CHN: *Anal. Calc.* for $\text{C}_{14}\text{H}_{19}\text{NO}_2$: C, 72.07%, H, 8.21%, N, 6.00%; Found: C, 72.20%, H, 8.19%, N, 5.89%.

3-Methyl-1-(4-morpholinophenyl)butan-1-one **6.34**

According to literature procedure 7.6.2 run for 48 hours with 5 mol% catalyst, the product was purified by silica column chromatography (eluent; hexanes/EtOAc, 0-100% over 60 min, det: KMnO_4) and isolated as a yellow crystalline solid (423 mg, 57%). m. p. = 72-74 °C; IR: $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 2959, 1659, 1595, 1516, 1449, 1364, 1218, 1181, 1125, 926, 815; ^1H NMR: (CDCl_3 , 300 MHz) $\delta = 7.90$ (2H, d, $J = 9.00$ Hz, H_6), 6.87 (2H, d, $J = 9.00$ Hz, H_7), 3.86 (4H, app. t, $J = 4.80$ Hz, H_{10}), 3.30 (4H, app. t, $J = 4.95$ Hz, H_9), 2.75 (2H, d, $J = 6.90$ Hz, H_2), 2.27 (1H, sept, $J = 6.60$ Hz, H_3), 0.98 (3H, d, $J = 6.6$ Hz, H_4); ^{13}C NMR: (CDCl_3 , 75.4 MHz) $\delta = 198.8$ (C_1), 154.2 (C_8), 130.3 (C_6), 128.5 (C_5), 113.4 (C_7), 66.7 (C_{10}), 47.7 (C_9), 47.1 (C_2), 25.7 (C_3), 23.0 (C_4); HRMS(ESI-TOF): calcd. for $\text{C}_{15}\text{H}_{21}\text{NO}_2\text{H}^+$: 248.1645. Found: 248.1718

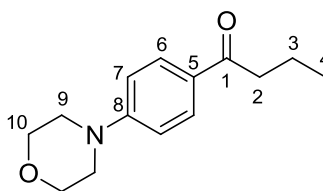
(MH^+), 270.1520 (MNa^+); CHN: *Anal. Calc.* for $\text{C}_{15}\text{H}_{21}\text{NO}_2$: C, 72.84%, H, 8.56%, N, 5.66%; Found: C, 72.80%, H, 8.66%, N, 5.56%.

1-(4-Morpholinophenyl)-3-phenylpropan-1-one **6.36**



According to literature procedure 7.6.2 run for 48 hours with 5 mol% catalyst, the product was purified by silica column chromatography (eluent; hexanes/EtOAc, 1:1, $R_f = 0.36$, det: KMnO_4) and isolated as an orange crystalline solid (328 mg, 37%). m. p. = 66-68 °C; IR: $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 2960, 2869, 2848, 1655, 1603, 1448, 1382, 1248, 1186, 1122, 1053, 926, 818, 696; ^1H NMR: (CDCl_3 , 300 MHz) $\delta = 7.90$ (2H, d, $J = 9.00$ Hz, H_9), 7.18-7.32 (5H, m, arom. H), 6.87 (2H, d, $J = 9.00$ Hz, H_{10}), 3.86 (4H, app. t, $J = 4.95$ Hz, H_{13}), 3.30 (4H, app. t, $J = 4.95$ Hz, H_{12}), 3.20-3.25 (2H, m, H_2), 3.03-3.08 (2H, m, H_3); ^{13}C NMR: (CDCl_3 , 75.4 MHz) $\delta = 197.6$ (C_1), 154.3 (C_{11}), 141.7 (C_4), 130.2 (C_9), 128.6 (C_6), 128.5 (C_5), 127.8 (C_7), 126.1 (C_8), 113.4 (C_{10}), 66.7 (C_{13}), 47.6 (C_{12}), 40.0 (C_2), 30.6 (C_3); HRMS(ESI-TOF): calcd. for $\text{C}_{19}\text{H}_{21}\text{NO}_2\text{H}^+$: 296.1651. Found: 296.1641 (MH^+); CHN: *Anal. Calc.* for $\text{C}_{19}\text{H}_{21}\text{NO}_2$: C, 77.26%, H, 7.17%, N, 4.74%; Found: C, 72.36%, H, 7.29%, N, 4.85%.

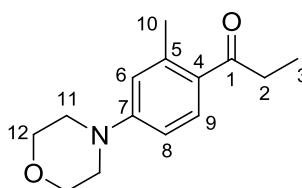
1-(4-Morpholinophenyl)-3-phenylpropan-1-one **6.37**



According to literature procedure 7.6.2, the product was purified by silica column chromatography (eluent; hexanes/EtOAc, 1:1, $R_f = 0.31$, det: KMnO_4) and isolated as a yellow crystalline solid (593 mg, 85%). m. p. = 67-69 °C; IR: $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 2965, 1665, 1594, 1219, 1186, 1123, 925, 818; ^1H NMR: (CDCl_3 , 300 MHz) $\delta = 7.90$ (2H, d, $J = 9.00$ Hz, H_6), 6.87 (2H, d, $J = 9.00$ Hz, H_7), 3.86 (4H, app. t, $J = 4.95$ Hz, H_{10}), 3.30 (4H, app. t, $J = 4.95$ Hz, H_9), 2.87 (2H, t, $J = 7.20$ Hz, H_2), 1.69-1.82 (2H, m,

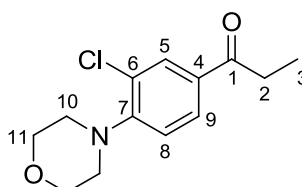
H₃), 0.99 (3H, t, $J = 7.50$ Hz, H₄); ¹³C NMR: (CDCl₃, 75.4 MHz) $\delta = 199.0$ (C₁), 154.2 (C₈), 130.2 (C₆), 128.2 (C₅), 113.5 (C₇), 66.7 (C₁₀), 47.7 (C₉), 40.2 (C₂), 18.3 (C₃), 14.1 (C₄); HRMS(ESI-TOF): calcd. for C₁₄H₁₉NO₂H⁺: 234.1489. Found: 234.1562 (MH⁺); CHN: *Anal. Calc.* for C₁₄H₁₉NO₂: C, 72.07%, H, 8.21%, N, 6.00%; Found: C, 72.04%, H, 8.25%, N, 5.99%.

1-(2-Methyl-4-morpholinophenyl)propan-1-one **6.44**



According to literature procedure 7.6.2, the product was purified by silica column chromatography (eluent; hexanes/EtOAc, 3:1, $R_f = 0.31$, det: KMnO₄) and isolated as a yellow crystalline solid (357 mg, 51%). m. p. = 69-70 °C; IR: $\nu_{\max}/\text{cm}^{-1}$ (neat) 2971, 1653, 1601, 1549, 1453, 1361, 1217, 1123, 1111, 1054, 967, 877, 785, 645; ¹H NMR: (CDCl₃, 300 MHz) $\delta = 7.72$ (1H, d, $J = 9.30$ Hz, H₉), 6.68-6.71 (2H, m, arom. H), 3.84 (4H, app. t, $J = 4.95$ Hz, H₁₂), 3.26 (4H, app. t, $J = 4.80$ Hz, H₁₁), 2.89 (2H, q, $J = 7.20$ Hz, H₂), 2.56 (3H, s, H₁₀), 1.17 (3H, t, $J = 7.50$ Hz, H₃); ¹³C NMR: (CDCl₃, 75.4 MHz) $\delta = 202.1$ (C₁), 152.9 (C₇), 141.7 (C₅), 131.7 (C₉), 127.8 (C₄), 117.5 (C₆), 110.9 (C₈), 66.7 (C₁₂), 47.8 (C₁₁), 33.5 (C₂), 23.1 (C₁₀), 8.9 (C₃); HRMS(ESI-TOF): calcd. for C₁₄H₁₉NO₂H⁺: 234.1494. Found: 234.1478 (MH⁺), 256.1291 (MNa⁺); CHN: *Anal. Calc.* for C₁₄H₁₉NO₂: C, 72.07%, H, 8.21%, N, 6.00%; Found: C, 72.00%, H, 8.10%, N, 5.93%.

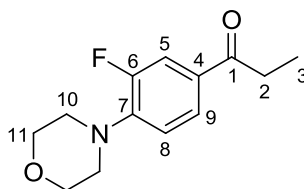
1-(3-Chloro-4-morpholinophenyl)propan-1-one **6.46**



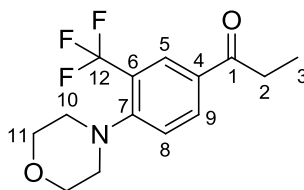
According to literature procedure 7.6.2, the product was purified by silica column chromatography (eluent; petroleum ether b. p. 40-60 °C/Et₂O, 2:1, $R_f = 0.36$, det: KMnO₄) and isolated as a yellow crystalline solid (560 mg, 58%). m. p. = 70-71 °C;

IR: $\nu_{\max}/\text{cm}^{-1}$ (neat) 2971, 1677, 1593, 1446, 1374, 1223, 1114, 1039, 965, 797, 690, 642; ^1H NMR: (CDCl_3 , 300 MHz) δ = 7.96 (1H, d, J = 2.10 Hz, H_5), 7.82 (1H, dd, J = 8.40 2.10 Hz, H_9), 7.02 (1H, d, J = 8.40 Hz, H_8), 3.87 (4H, app. t, J = 4.65 Hz, H_{11}), 3.13-3.16 (4H, m, H_{10}), 2.92 (2H, q, J = 7.20 Hz, H_2), 1.20 (3H, t, J = 7.20 Hz, H_3); ^{13}C NMR: (CDCl_3 , 75.4 MHz) δ = 198.8 (C_1), 152.9 (C_7), 132.3 (C_6), 131.0 (C_5), 128.2 (C_4), 127.9 (C_9), 119.6 (C_8), 67.0 (C_{11}), 51.3 (C_{10}), 31.7 (C_2), 8.4 (C_3); HRMS(ESI-TOF): calcd. for $\text{C}_{13}\text{H}_{16}\text{ClNO}_2\text{H}^+$: 254.0948. Found: 254.0920 (MH^+), 276.0740 (MNa^+); CHN: *Anal. Calc.* for $\text{C}_{13}\text{H}_{16}\text{ClNO}_2$: C, 61.54%, H, 6.36%, N, 5.52%; Found: C, 61.39%, H, 6.39%, N, 5.42%.

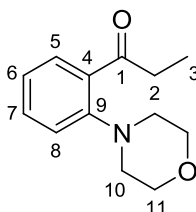
1-(3-Fluoro-4-morpholinophenyl)propan-1-one **6.47**



According to literature procedure 7.6.2, the product was purified by silica column chromatography (eluent; petroleum ether b. p. 40-60 °C/ Et_2O , 1:1, R_f = 0.33, det: KMnO_4) and isolated as a yellow crystalline solid (479 mg, 67%). m. p. = 116-117 °C; IR: $\nu_{\max}/\text{cm}^{-1}$ (neat) 2857, 1675, 1611, 1562, 1517, 1382, 1248, 1110, 1048, 923, 883, 796; ^1H NMR: (CDCl_3 , 300 MHz) δ = 7.69 (1H, dd, J = 8.40 2.10 Hz, H_9), 7.63 (1H, dd, J = 14.10 2.10 Hz, H_5), 6.90 (1H, app. t, J = 8.40 Hz, H_8), 3.86 (4H, app. t, J = 4.80 Hz, H_{11}), 3.19 (4H, app. t, J = 4.65 Hz, H_{10}), 2.91 (2H, q, J = 7.20 Hz, H_2), 1.20 (3H, t, J = 7.20 Hz, H_3); ^{13}C NMR: (CDCl_3 , 75.4 MHz) δ = 198.7 (d, J = 1.7 Hz, C_1), 154.7 (d, J = 246.7 Hz, C_6), 143.9 (d, J = 8.2 Hz, C_4), 131.0 (d, J = 6.0 Hz, C_7), 125.2 (d, J = 3.0 Hz, C_9), 117.5 (d, J = 3.2 Hz, C_8), 116.0 (d, J = 21.9 Hz, C_5), 66.9 (C_{11}), 50.3 (d, J = 4.4 Hz, C_{10}), 31.6 (C_2), 8.5 (C_3); ^{19}F NMR: (CDCl_3 , 376 MHz) δ = -121.5 (dd, J = 13.9 8.6 Hz); HRMS(ESI-TOF): calcd. for $\text{C}_{13}\text{H}_{16}\text{FNO}_2\text{H}^+$: 238.1243. Found: 238.1227 (MH^+), 260.1038 (MNa^+); CHN: *Anal. Calc.* for $\text{C}_{13}\text{H}_{16}\text{FNO}_2$: C, 65.81%, H, 6.80%, N, 5.90%; Found: C, 66.01%, H, 6.90%, N, 5.91%.

1-(4-Morpholino-3-(trifluoromethyl)phenyl)propan-1-one **6.48**

According to literature procedure 7.6.2, the product was purified by silica column chromatography (eluent; hexanes/EtOAc, 4:1, $R_f = 0.13$, det: KMnO_4) and isolated as a yellow crystalline solid (525 mg, 61%). m. p. = 62-64 °C; IR: $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 2978, 1678, 1602, 1501, 1457, 1318, 1235, 1209, 1114, 1092, 1040, 924, 801, 663; ^1H NMR: (CDCl_3 , 300 MHz) δ = 8.23 (1H, d, $J = 2.10$ Hz, H_5), 8.11 (1H, d, $J = 8.40$ Hz, H_9), 7.32 (1H, d, $J = 8.40$ Hz, H_8), 3.85 (4H, app. t, $J = 4.50$ Hz, H_{11}), 2.95-3.04 (6H, m, H_{10} & H_2), 1.23 (3H, t, $J = 7.20$ Hz, H_3); ^{13}C NMR: (CDCl_3 , 75.4 MHz) δ = 198.9 (C_1), 155.7 (d, $J = 1.1$ Hz, C_7), 132.6 (C_9), 132.5 (C_4), 128.2 (q, $J = 5.4$ Hz, C_5), 125.8 (d, $J = 29.6$ Hz, C_6), 123.9 (q, $J = 273.3$ Hz, C_{12}), 122.8 (C_8), 67.2 (C_{11}), 53.4 (C_{10}), 31.8 (C_2), 8.3 (C_3); ^{19}F NMR: (CDCl_3 , 376 MHz) δ = -60.1 (s); HRMS(ESI-TOF): calcd. for $\text{C}_{14}\text{H}_{16}\text{F}_3\text{NO}_2\text{Na}^+$: 310.1025. Found: 310.1115 (MNa^+); CHN: Anal. Calc. for $\text{C}_{14}\text{H}_{16}\text{F}_3\text{NO}_2$: C, 58.53%, H, 5.61%, N, 4.88%; Found: C, 58.50%, H, 5.45%, N, 4.64%.

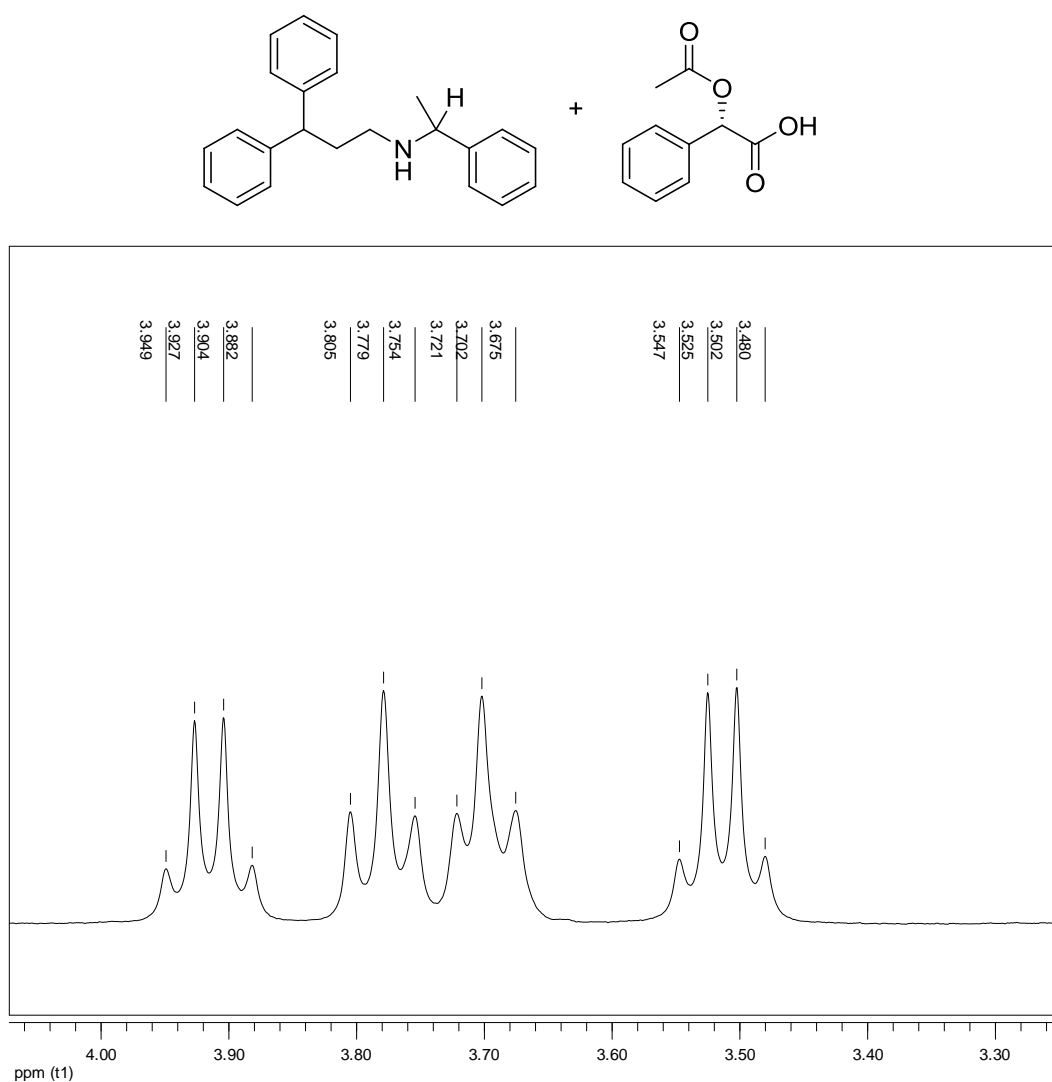
1-(2-Morpholinophenyl)propan-1-one **6.49**

According to literature procedure 7.6.2 with 5 mol% catalyst for 48 hours, the product was purified by silica column chromatography (eluent; cyclohexane/EtOAc, 0-100%, det: KMnO_4) and isolated as a yellow oil (230 mg, 35%). IR: $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 2966, 2854, 1680, 1593, 1484, 1445, 1223, 1207, 1115, 929, 921, 758; ^1H NMR: (CDCl_3 , 300 MHz) δ = 7.40 (1H, t, $J = 7.80$ Hz, H_5), 7.32 (1H, d, $J = 8.10$ Hz, H_7), 7.06-7.11 (2H, m, arom. H), 3.82 (4H, app. t, $J = 4.50$ Hz, H_{11}), 3.05 (2H, q, $J = 7.20$ Hz, H_2), 2.97 (4H, app. t, $J = 4.50$ Hz, H_{10}), 1.17 (3H, t, $J = 7.20$ Hz, H_3); ^{13}C NMR: (CDCl_3 , 75.4 MHz) δ = 208.7 (C_1), 150.6 (C_9), 136.2 (C_4), 131.5 (C_7), 128.8 (C_5),

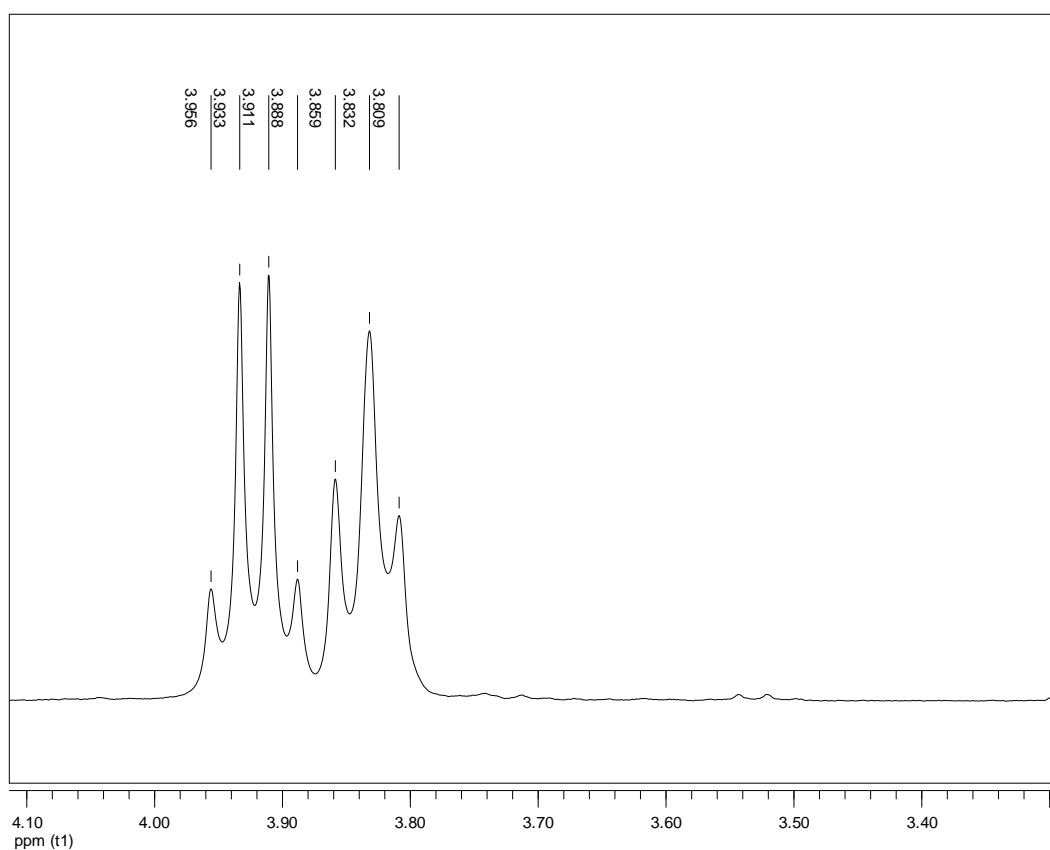
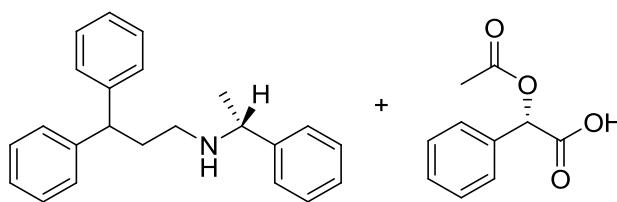
123.3 (C₈), 118.8 (C₆), 67.2 (C₁₁), 53.4 (C₁₀), 35.3 (C₂), 8.8 (C₃); HRMS(ESI-TOF): calcd. for C₁₃H₁₇NO₂Na⁺: 242.1157. Found: 242.1196 (MNa⁺); CHN: *Anal. Calc.* for C₁₃H₁₇NO₂: C, 77.38%, H, 8.81%, N, 6.45%; Found: C, 77.25%, H, 8.96%, N, 6.61%.

7.7 Relevant NMR Spectra

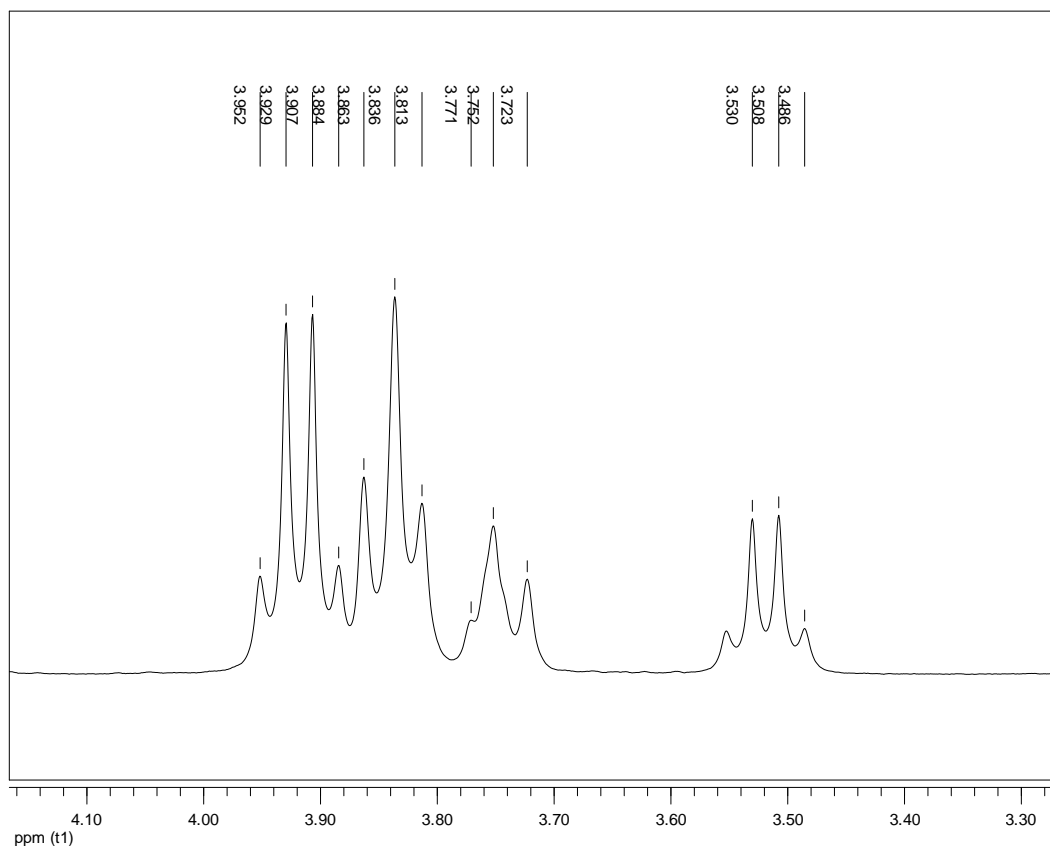
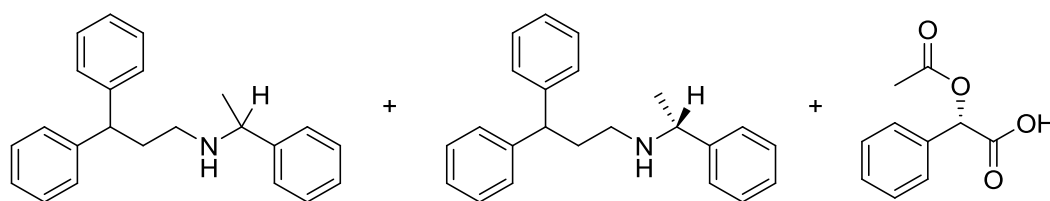
7.7.1 Racemic Fendiline (2.52) + (*S*)-*O*-Acetylmandelic Acid



According to representative procedure 7.2.3, the sample run on a 300 MHz NMR machine. Analysis of the peaks above show that there are two compounds present, with the hydrogen atom indicated in the diagram present at 3.92 ppm and 3.51 ppm. For reference, the quoted shift for this proton in both Fendiline (**2.52**) and (*R*)-Fendiline (**2.56**) is 3.68 ppm.

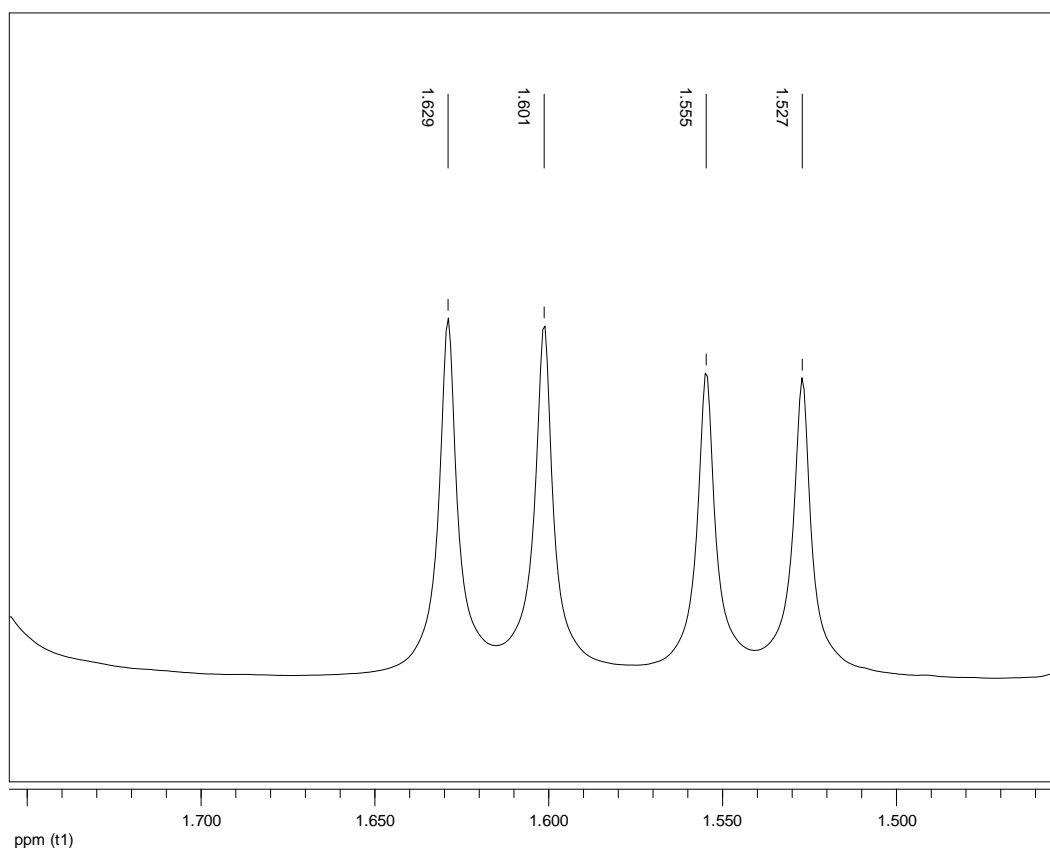
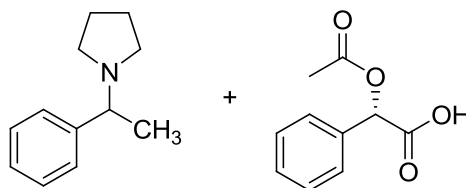
7.7.2 (*R*)-Fendiline (2.56) + (*S*)-O-Acetylmandelic Acid

According to representative procedure 7.2.3, the sample run on a 300 MHz NMR machine. Analysis of the peaks above show that there is only one compound present, with the hydrogen atom indicated in the diagram present at 3.92 ppm and there is no peak at 3.51 ppm as seen in the case of the racemic sample (7.7.1). For reference, the quoted shift for this proton in both Fendiline (2.52) and (*R*)-Fendiline (2.56) is 3.68 ppm.

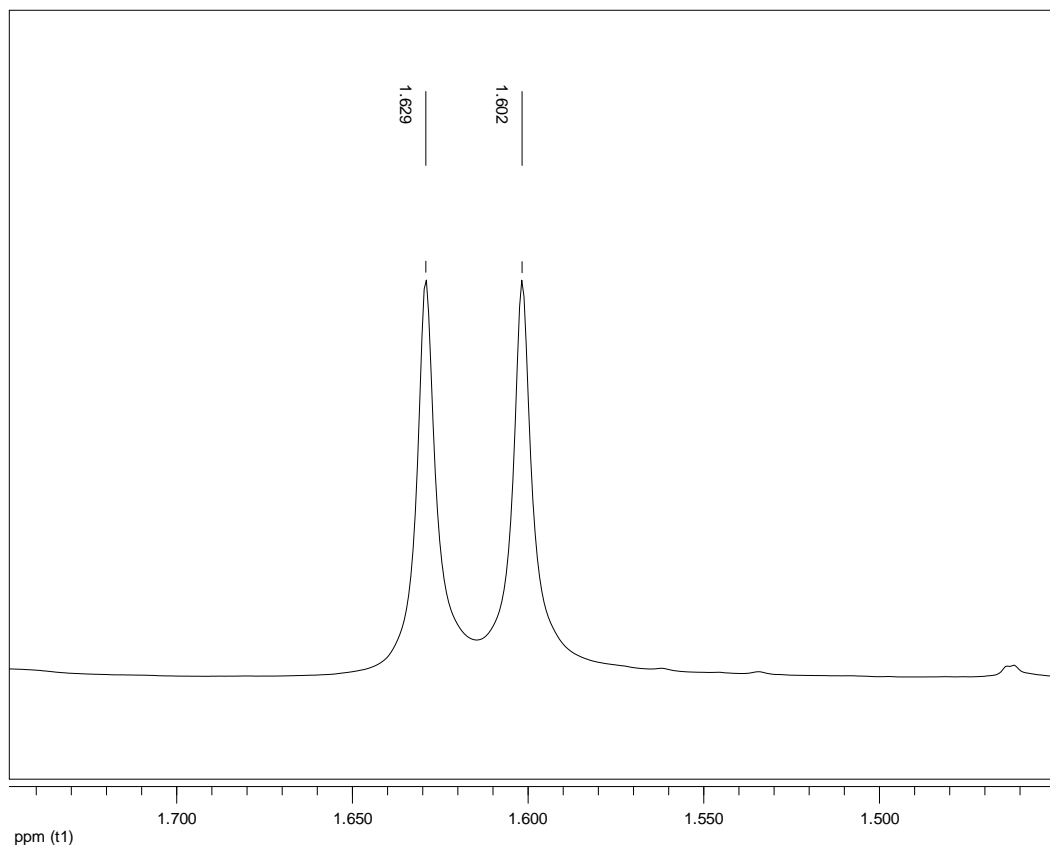
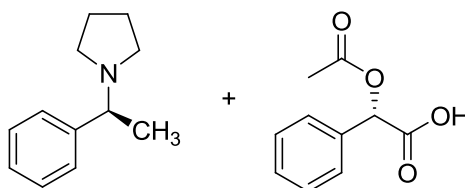
7.7.3 Fendiline (2.52) + (*R*)-Fendiline (2.56) + (*S*)-O-Acetylmandelic Acid

According to representative procedure 7.2.3, the sample run on a 300 MHz NMR machine. Analysis of the peaks above show that there are two compounds present, with the hydrogen atom indicated in the diagram present at 3.92 ppm and at a lower intensity 3.51 ppm. For reference, the quoted shift for this proton in both Fendiline (2.52) and (*R*)-Fendiline (2.56) is 3.68 ppm.

7.7.4 Racemic 1-(Phenethyl)pyrrolidine (3.22) + (*S*)-*O*-Acetylmandelic Acid

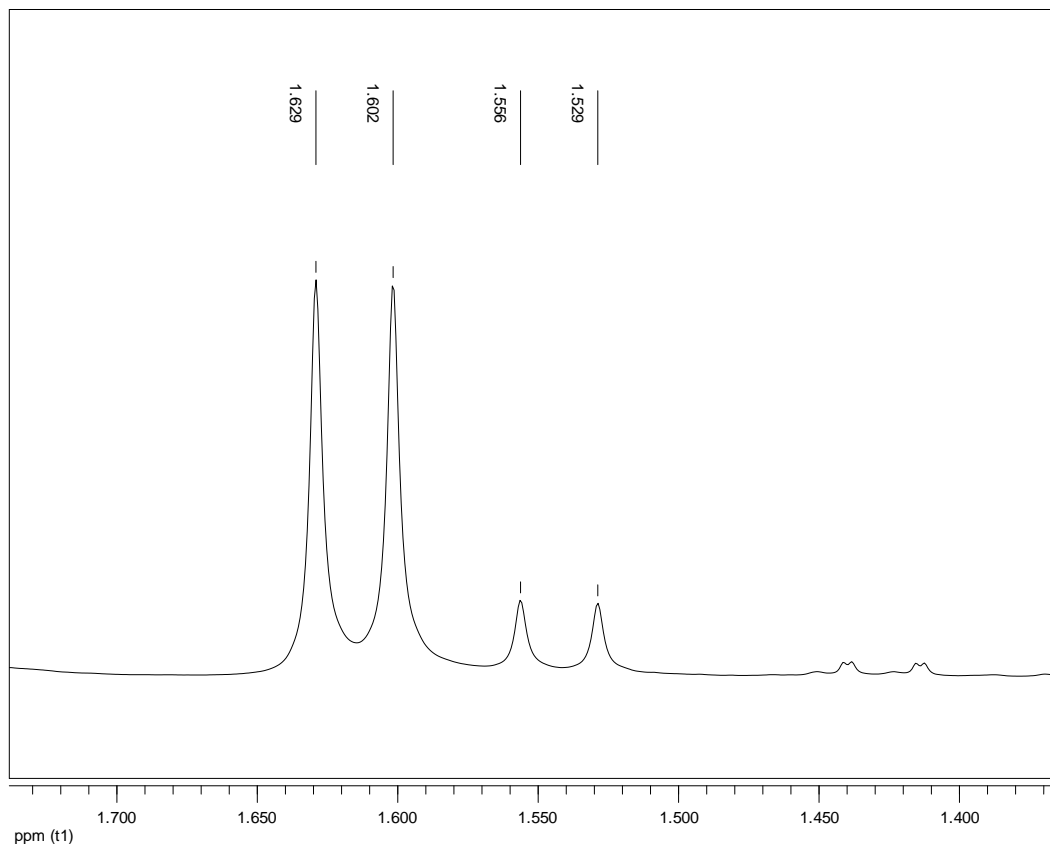
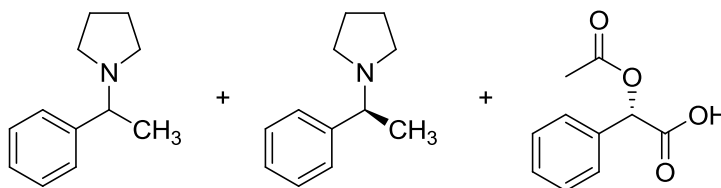


According to representative procedure 7.2.3, the sample run on a 300 MHz NMR machine. Analysis of the peaks above show that there are two compounds present, with the methyl group indicated in the diagram present at 1.62 ppm and 1.54 ppm. For reference, the quoted shift for this proton in both 1-(phenethyl)pyrrolidine (**3.22**) and (*S*)-1-(phenethyl)pyrrolidine (**3.23**) is 1.34 ppm.

7.7.5 (*S*)-1-(Phenethyl)pyrrolidine (3.23) + (*S*)-O-Acetylmandelic Acid

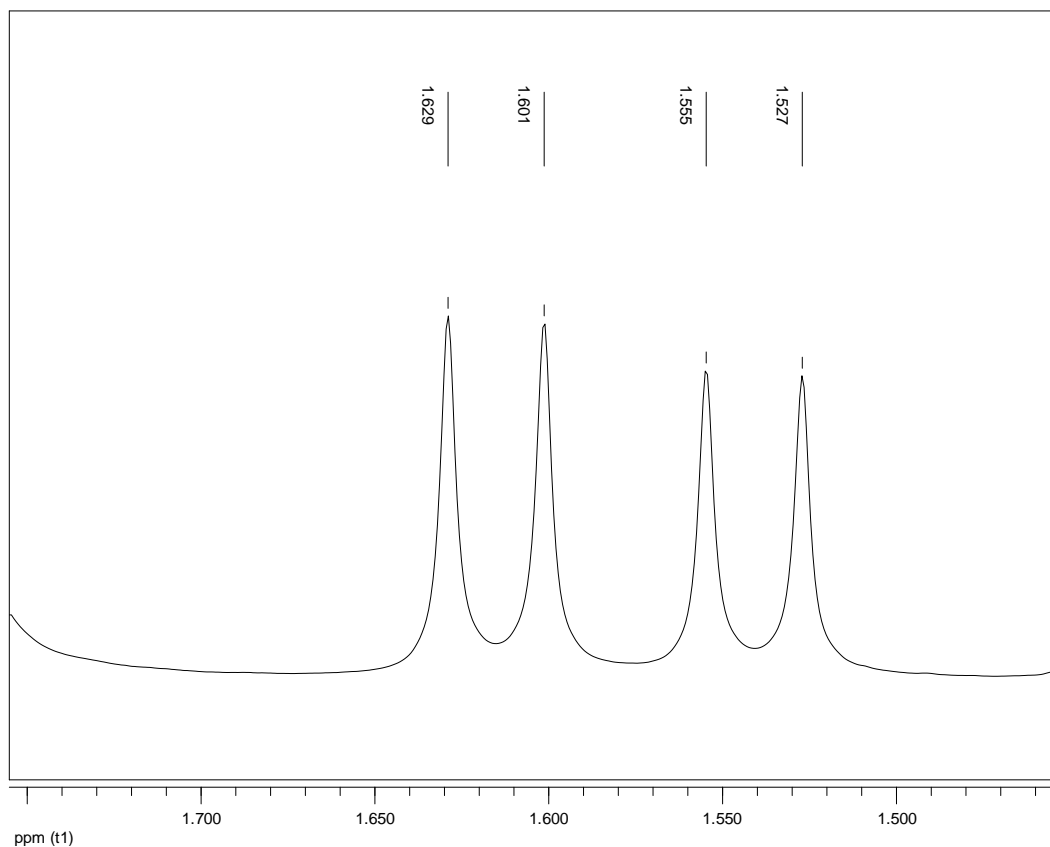
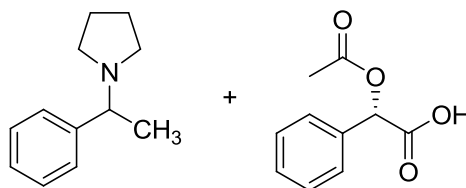
According to representative procedure 7.2.3, the sample run on a 300 MHz NMR machine. Analysis of the peaks above show that there is only one compound present, with the hydrogen atom indicated in the diagram present at 1.61 ppm and there is no peak at 1.54 ppm as seen in the case of the racemic sample (7.7.4). For reference, the quoted shift for this proton in both 1-(phenethyl)pyrrolidine (3.22) and (*S*)-1-(phenethyl)pyrrolidine (3.23) is 1.34 ppm.

**7.7.6 1-(Phenethyl)pyrrolidine (3.22) + (S)-1-(Phenethyl)pyrrolidine (3.23)
+ (S)-O-Acetylmandelic Acid**

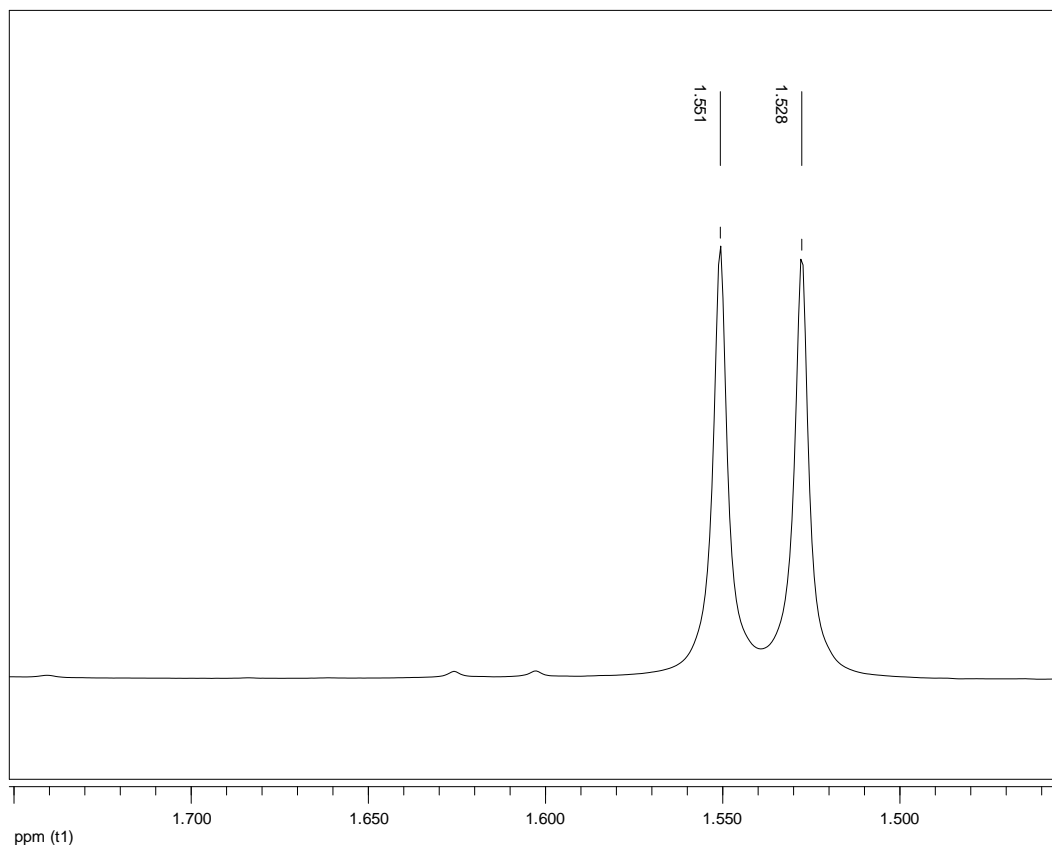
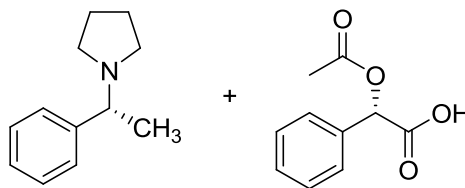


According to representative procedure 7.2.3, the sample run on a 300 MHz NMR machine. Analysis of the peaks above show that there are two compounds present, with the hydrogen atom indicated in the diagram present at 1.61 ppm and at a lower intensity 1.54 ppm. For reference, the quoted shift for this proton in both 1-(phenethyl)pyrrolidine (**3.22**) and (S)-1-(phenethyl)pyrrolidine (**3.23**) is 1.34 ppm.

7.7.7 Racemic 1-(Phenethyl)pyrrolidine (4.22) + (S)-O-Acetylmandelic Acid



According to representative procedure 7.2.3, the sample run on a 300 MHz NMR machine. Analysis of the peaks above show that there are two compounds present, with the methyl group indicated in the diagram present at 1.62 ppm and 1.54 ppm. For reference, the quoted shift for this proton in both 1-(phenethyl)pyrrolidine (**3.22**) and (*R*)-1-(phenethyl)pyrrolidine (**4.29**) is 1.34 ppm.

7.7.8 (*R*)-1-(Phenethyl)pyrrolidine (**4.29**) + (*S*)-*O*-Acetylmandelic Acid

According to representative procedure 7.2.3, the sample run on a 300 MHz NMR machine. Analysis of the peaks above show that there is only one compound present, with the hydrogen atom indicated in the diagram present at 1.61 ppm and there is no peak at 1.54 ppm as seen in the case of the racemic sample (**7.7.4**). For reference, the quoted shift for this proton in both 1-(phenethyl)pyrrolidine (**3.22**) and (*S*)-1-(phenethyl)pyrrolidine (**4.29**) is 1.34 ppm.

7.8 References

- [1] Akisanya, J.; Danks, T. N.; Garman, R. N. *J. Organomet. Chem.*, **2000**, *603*, 240-243.
- [2] Langeron, M.; Fleury, M.-B. *Org. Lett.* **2009**, *11*, 883-886.
- [3] Hanada, S.; Ishida, T.; Motoyama, Y.; Nagashima, H. *J. Org. Chem.* **2007**, *72*, 7551-7559.
- [4] Kawahara, R.; Fujita, K.; Yamaguchi, R. *J. Am. Chem. Soc.* **2010**, *132*, 15108-15111.
- [5] Hanada, S.; Tsutsumi, E.; Motoyama, Y.; Nagashima, H. *J. Am. Chem. Soc.* **2009**, *131*, 15032-15040.
- [6] Wiseman, L. R.; Johnson, S. M.; Kelker, M. S.; Foss, T.; Wilson, I. A.; Kelly, J. W., *J. Am. Chem. Soc.* **2005**, *127*, 5540-5551.
- [7] Morcuende, A.; Ors M.; Valverde, S.; Herradn, B. *J. Org. Chem.* **1996**, *61*, 5264-5270.
- [8] Purchase II, C. F.; Goel, O. P. *J. Org. Chem.* **1991**, *56*, 457-459.
- [9] Byschauer, A.; Friese-Kimmel, A.; Baumann, G.; Schunack, W. *Eur. J. Med. Chem.*, **1992**, *27*, 321-330.
- [10] Takeuchi, K.; Kohn, T. J.; True, T. A.; Mais, D. E.; Wikel, J. H.; Utterback, B. G.; Wyss, V. L.; Jakubowski, J. A. *J. Med. Chem.* **1998**, *41*, 5362-5374.
- [11] Campos, K. R.; Cai, D.; Journet, M.; Kowal, J. J.; Larsen, R. D.; Reider, P. J. *J. Org. Chem.*, **2001**, *66*, 3634-3635.
- [12] Gunanathan, C.; Milstein, D. *Angew. Chem. Int. Ed.* **2008**, *47*, 8661-8664.
- [13] Saidi, O.; Blacker, A. J.; Farah, M. M.; Marsden, S. P.; Williams, J. M. J. *Chem. Commun.* **2010**, *46*, 1541-1543.
- [14] Rische, T.; Eilbracht, P. *Tetrahedron* **1999**, *55*, 1915-1920.
- [15] Fujita, K.; Fujii, T.; Yamaguchi, R., *Org. Lett.* **2004**, *6*, 3525-3528.
- [16] Brenner, E.; Schnieder, R.; Fort, Y. *Tetrahedron*, **1999**, *55*, 12829-12842.

- [17] Verardo, G.; Dolce, A.; Toniutti, N.; *Synthesis*, **1999**, 1, 74-79.
- [18] Xu, L.; Zhu, D.; Wan, F.; Wang, R.; Wan, B., *Tetrahedron*, **2005**, 61, 6553-6560.
- [19] Zakrzewska, A.; Kolehmainen, E.; Osmialowski, B.; Gawinecki, R. *J. Fluorine Chem.* **2001**, 111, 1-10.
- [20] Xu, G.; Wang, Y-G., *Org. Lett.* **2004**, 6, 985-987.
- [21] Wolfe, J. P., Buchwald, S. L., *J. Org. Chem.* **1997**, 62, 1264-1267.
- [22] Ju, Y.; Varma, R. S. *Org. Lett.* **2005**, 7, 2409-2411.
- [23] Lee, S. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, 116, 5985-5986.
- [24] Sugiyama, S.; Morishita, K.; Chiba, M.; Ishii, K. *Heterocycles* **2002**, 57, 637-648.
- [25] Heaney, H.; Papageorgiou, G.; Wilkins, R. F. *Tetrahedron* **1997**, 53, 2941-2958.
- [26] Legault, C.; Charette, A. B. *J. Org. Chem.* **2003**, 68, 7119-7122.
- [27] Quach, T. D.; Batey, R. A. *Org. Lett.* **2003**, 5, 4397-4400.
- [28] Shim, S. C.; Doh, C. H.; Kim, T. J.; Lee, H. K.; Kim, K. D. *J. Het. Chem.* **1988**, 25, 1383-1385.
- [29] Ohsawa, T.; Ihara, M.; Fukumoto, K. *J. Org. Chem.* **1983**, 48, 3644-3648.
- [30] Šukalović, V.; Roglić, G.; Husinec, S.; Kostić-Rajačić, S.; Andrić, D.; Šoškić, V. *Arch. Pharm. Pharm. Med. Chem.* **2003**, 336, 514-522.
- [31] Hamid, M. H. S. A.; Allen, C. A.; Lamb, G. W.; Maytum, H. C.; Maxwell, A. C.; Watson, A. J. A.; Williams, J. M. J. *J. Am. Chem. Soc.* **2009**, 131, 1766-1774.
- [32] Tillack, A.; Hollman, D.; Mevius, K.; Michalik, D.; Bähn, S.; Beller, M. *Eur. J. Org. Chem.* **2008**, 4745-4750.
- [33] Harris, C. E.; Fisher, G. B.; Beardsley, D.; Lee, L.; Goralski, C. T.; Nicholson, L. W.; Singaram, B. *J. Org. Chem.*, **1994**, 59, 7746-7751.

- [34] Crecente-Campo, J.; Vázquez-Tato, M. P.; Seijas, J. A. *Tetrahedron*, **2009**, *65*, 2655-2659.
- [35] Zhu, X.; Su, L.; Huang, L.; Chen, G.; Wang, J.; Song, H.; Wan, Y. *Eur. J. Org. Chem.* **2009**, *5*, 635-642.
- [36] Bähn, S.; Hollmann, D.; Tillack, A.; Beller, M. *Adv. Synth. Catal.* **2008**, *350*, 2099-2103.
- [37] Malkov, A. V.; Mariani, A.; MacDougall, K. N.; Kočovský, P. *Org. Lett.* **2004**, *6*, 2253-2256.
- [38] Poleschner, H.; Seppelt, K. *Chem. Eur. J.* **2004**, *10*, 6565-6574.
- [39] Rad, M. N. S.; Khalafi-Nezhad, A.; Asrari, Z.; Behrouz, S.; Amini, Z.; Behrouz, M. *Synthesis*, **2009**, *23*, 3983-3988.
- [40] Li, J.; Xu, F.; Zhang, Y.; Shen, Q. *J. Org. Chem.* **2009**, *74*, 2575-2577.
- [41] Ishihara, K.; Yano, T. *Org. Lett.* **2004**, *6*, 1983-1986.
- [42] Sambrook, M. R.; Beer, P. D.; Wisner, J. A.; Paul, R. L.; Cowley, A. R.; Szemes, F.; Drew, M. G. B. *J. Am. Chem. Soc.* **2005**, *127*, 2292-3302.
- [43] Zyryanov, G. V.; Rudkevich, D. M. *Org. Lett.* **2003**, *5*, 1253-1256.
- [44] Saidi, O.; Blacker, A. J.; Lamb, G. W.; Marsden, S. P.; Taylor, J. E.; Williams, J. M. J. *Org. Process Res. & Dev.* **2010**, *14*, 1046-1049.
- [45] Chen, T.; Jiang, J.-J.; Xu, Q.; Shi, M. *Org. Lett.* **2007**, *9*, 865-868.
- [46] Zhang, X.; Corma, A. *Chem. Commun.* **2007**, 3080-3082.
- [47] Pickard, S. T.; Smith, H. E. *J. Am. Chem. Soc.* **1990**, *112*, 5741-5747.
- [48] Handa, S.; Jones, K.; Newton, C. G.; *J. Chem. Soc. Perk. T. 1*, **1995**, *12*, 1623-1634.
- [49] Vázquez, M. T.; Rosell, G.; Pujol, M. D. *Eur. J. Med. Chem.* **1997**, *32*, 529-534.
- [50] ten Brink, G.-J.; Arends, I. W. C. E.; Sheldon, R. A. *Adv. Synth. Catal.* **2002**, *344*, 355-369.

- [51] Hatano, M.; Suzuki, S.; Ishihara, K. *J. Am. Chem. Soc.* **2006**, *128*, 9998-9999.
- [52] Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N.; Murai, S. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 62-83.
- [53] Jun, C.-H.; Moon, C. W.; Hong, J.-B.; Lim, S.-G.; Chung, K.-Y.; Kim, Y.-H. *Chem. Eur. J.* **2002**, *8*, 485-492.
- [54] Kim, M.; Chang, S. *Org. Lett.* **2010**, *12*, 1640-1643.
- [55] Castro, L. C. M.; Bézier D.; Sortais, J.-B.; Darcel, C. *Adv. Synth. Catal.* **2011**, *353*, 1279-1284.
- [56] Maytum, H. C.; Francos, J.; Whatrup, D. J; Williams, J. M. J. *Chem. Asian J.* **2010**, *5*, 538-542.
- [57] Evans, P.; Johnson, P.; Taylor, R. J. K. *Eur. J. Org. Chem.* **2006**, *7*, 1740-1754.
- [58] Zhang, Li.; Zha, Z.; Zhang, Z.; Li, Y.; Wang, Z. *Chem. Commun.* **2010**, 7196-7198.
- [59] Bruce, R. A.; Nago, T. *J. Heterocyclic Chem.* **2009**, *46*, 623-628.

APPENDIX